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The Turkish Journal of Pediatrics
P.K. 66, 06240 Samanpazarı, Ankara, Turkey
Telephone : (312) 324 42 91
Fax : (312) 324 32 84

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TOBACCO: A FUTURE DISASTER FOR TURKEY'S CHILDREN*

*John Crofton MD***

SUMMARY: Crofton J. (University of Edinburgh, Edinburgh, Scotland). Tobacco: a future disaster for Turkey's children. Turk J Pediatr 1996; 38: 1-11.

Limited data from Turkey indicate that smoking presents a major threat to Turkish children. Parental, particularly maternal, smoking results in an increase in spontaneous abortion, low birth weight, congenital abnormalities, neonatal death and decreased physical and mental development in the infant, which can persist into adult life. Parental smoking results in increased rates of respiratory and middle ear illness in children, more so in infants and in older children more school absences. Naturally both of the effects are even greater if the children start to smoke themselves. Smoking parents are more likely to have smoking children, so that the cycle of illness repeats in future generations. Doctors have a major responsibility to save both present and future generations from this disaster. In this article appropriate action is outlined. *Key words: tobacco, Turkey, smoking children, smoking parents.*

In developed countries which have had a smoking problem for a long time the findings may be summarized as follows:

1. Almost all smoking starts before the age of twenty, mostly before the age of seventeen.
2. About half of all smoking young men well be killed by smoking-related diseases, 84 percent of them between the ages of 35 and 69. Probably the same will apply in due course to women, who have not been smoking so extensively for as long.
3. Maternal smoking leads to higher abortion rates, higher neonatal and infant death rates, more congenital abnormalities, and poorer physical and mental development in the child.
4. Parental smoking leads to increased respiratory ill-health in children.
5. Smoking in children leads to more respiratory illnesses and more school absences.
6. Smoking children become smoking adults, who become smoking parents, who are more likely to have smoking children, with all the resulting disease and death.

All this disaster can be prevented. Doctors must take the lead in that prevention.

Smoking in Turkey already presents a formidable problem. The rates in men are reportedly 63 percent and in women 24 percent, with somewhat similar rates in urban and rural areas. (Ministry of Health figures kindly provided by Professor Dagli).

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* From the University of Edinburgh, Edinburgh, Scotland.

** Professor Emeritus, University of Edinburgh, Edinburgh, Scotland.

From the İhsan Doğramaası Honorary Lecture given at the Institute of Child Health, Hacettepe University, October 1995.

Professor Dagli has provided me with some figures for children in Turkey. Twenty percent of boys aged eight to 12 have tried smoking. In secondary schools 33 percent of children smoke, more boys than girls. Only 25 percent of Turkish homes are said to be smoke-free, according to local not national surveys.

In the remainder of this lecture I will produce some samples of research evidence to support the above statements. I will then go on to suggest what we should all be doing to prevent this lethal epidemic.

Effects of Maternal Smoking

Spontaneous Abortion Rates: Spontaneous abortion rates increase with age. A survey by Himmelberger et al. (1978)[1] on nearly 13.000 women showed that for each age-group the abortion rates were higher in smokers than in non-smokers. At the extremes of the age range the respective rates were 19% and 15% for women less than 25 years old and 36% and 33% for those over 40.

Low Birth Weight: Haddow et al. (1978)[2] showed that there is a steady increase in the percentage of children with birth weights under 2800 g with increases in the amount smoked, up to those smoking 17 cigarettes a day. The percentage with low birth weight was 7.7 percent for non-smokers, rising to a peak of 22.9 percent for those smoking 13 to 17 cigarettes daily.

Congenital Abnormalities: In the study by Himmelberger et al[1]. already quoted, in each age group the percentage of congenital abnormalities was higher in smokers than in non-smokers. Again quoting the ends of the age range, in those under 25 the respective rates were 8.5% and 7.2% and in those over 40, 11.4 and 5.2 percent.

Late Fetal and Neonatal Death Rates Related to Smoking After the Fourth Month of Pregnancy: Haddow et al. (1987)[2] found an increasing rate with increased cigarette consumption. The rate was 32 per 1.000 in non-smokers, increasing to a peak of 42 in those smoking 10 or more cigarettes per day.

Effect of Smoking on Physical and Mental Development of the Infant: A number of studies have shown impairment of physical and mental development in infants of smoking mothers compared to infants of non-smokers. One of the most impressive demonstrations of this was in a cohort of 8.200 infants born in a single week in the UK and followed up for 23 years[3]. At certain intervals, height and mental achievement were measured. It is remarkable that the effect of maternal smoking was still demonstrated in these children when they reached the age of 23, after careful adjustment for other potentially confounding variables. With the increase in numbers of cigarettes smoked by the pregnant mother 23 years before, there was a steady decrease in their children's heights. For mothers who had smoked 20 cigarettes or more per day, the 23-year-old men were 0.41 and the 23-year-old women 1.49 cm below the mean height for the group. All the differences were highly statistically significant.

For mental ability the authors used a somewhat complicated formula to express academic qualifications after adjusting for known confounding factors such as social class and the size of the family. When the mothers had been non-smokers the mean positive qualification standards for the 23-year-olds were 0.25 for men and 0.35 for women. When the mother had smoked 20 cigarettes or more per day the negative figures were 0.77 and 1.09 respectively. Again the differences were highly significant.

Children's Illnesses and Smoking

Effects of Parental Smoking on Children's Illnesses: Table I summarizes a very useful review of this subject[4] A large number of studies have demonstrated a 50 to 100 percent excess, in children of smokers compared to children of non-smokers, of 1. acute respiratory infections; 2. cough, sputum and wheezing; and 3. middle ear disease. In the first two of these conditions the rates were even higher in infants. Asthmatic children of smokers have worse lung function, more frequent and more severe attacks than asthmatic children of non-smokers.

Table I: Children's Illnesses vs Parental Smoking

Illness	No. of Studies	Increased Risk	Higher
Acute Respiratory Infections	20	50-100%	Infants Mother smoking
Cough, Sputum Wheezing	26	50-100%	Infants
Asthma	10	More attacks More severe Worse lung function	
Middle Ear Disease	15	50%	

School Absences: One study of 2.885 children aged 12 to 13 year in the UK examined both the effects of childrens' smoking and that of their parents on the rate of school absences[5]. For boys the rate in those smoking regularly was 47 percent compared to 21 percent in the non-smokers. For girls the rates were 37% and 17%, respectively.

For non-smoking children where both parents were non-smokers or only the father smoked, the rate was 17% compared to 21% when both parents smoked or only the mother smoked.

Adolescents: In one of the studies where a cohort of children was followed from birth, it was found that smokers at age 20 had a substantially higher rate of cough day or night than non-smokers[6]. For men the rate in smokers was 13.9 percent compared to 3.2 percent in non-smokers. For women the rates were 16.0 and 6.5 percent, respectively.

In 195 boys aged 16 to 20, Backhouse showed a slight but steady decrease in lung function, as shown by the Peak Expiratory Flow Rate (PEFR), with

increasing daily consumption of cigarettes[7]. In the same age-group, improvement of PEFR was shown at each smoking rate when the 16-20-year-old boys were detained in a corrective institution where they were not allowed to smoke. The improvement in PEFR was 3.8 percent in the non-smokers, rising to 6.5 percent in those who had smoked 40 or more cigarettes a day[8].

The Vicious Family Circle[9] : From the above it can be seen that a smoking mother is liable to have a child with fetal problems leading in turn to increased neonatal and infant problems, leading in turn to developmental problems. A smoking mother is liable to have a smoking child, with the related increase in illnesses which I have described above. A smoking child is liable to go on to become a smoking adult with all the illnesses and death that this produces. The smoking adult then in turn becomes the smoking parent and the sad cycle is renewed in the next generation.

Prevention

Social Factors Affecting Smoking Prevalence: Positive factors tending to decrease smoking prevalence include:

1. Knowledge of the disastrous health effects.
2. Knowledge of the dangers of environmental smoke. I have demonstrated the effect on children, but of course the risks on environmental smoke in producing lung cancer in non-smokers is now well established[4].
3. The "top down" social pressure. Smoking often starts in the more prosperous and better educated members of the community and then gradually becomes adopted by the less educated and the poor. As the better educated become aware of the dangers, they start to abandon smoking. Gradually in this group smoking ceases to be socially acceptable. That process then very gradually moves down through the other social groups.

Counteracting these positive factors are the influences which tend to recruit new smokers among children, thus maintaining and increasing smoking prevalence:

1. The ruthless and highly successful promotion by the tobacco industry. I believe this is an expanding threat in Turkey.
2. The industry seeks to promote an image of manliness connected with smoking, which will appeal to boys and encourage them to take up the habit. Similarly it seeks to promote an image of glamour connected with smoking which will appeal to girls. With the low smoking rate in women in countries that are at an early stage in the smoking epidemic, the industry sees an enormous potential market among girls and women. This is being intensively exploited, particularly in Asia. The industry has to recruit children to smoking in order to replace those killed every day by the habit.

3. In a country like the UK, which is in an advanced stage of the smoking epidemic, the educated classes have steadily abandoned the habit, which is now increasingly socially unacceptable. For the less educated and the "non-achievers", either in school or in the adult population, smoking may form a sign of "tribal" cohesion among those who feel excluded from the more prosperous groups in society.
4. For very poor sections of the community, living in grim conditions, smoking may be regarded as one of the "escapes". Some mothers state, "It is my one luxury". When tomorrow seems hopeless, the prospect of future ill-health from cigarette smoking may seem relatively unimportant.

All these negative effects need countering. It is logically absurd that a habit which we now know is liable to kill one in two of those who take it up[10] should be permitted by any responsible government to promote their lethal products to the public. The industry has all the money in the world, but doctors have all the morality on their side. We must win in the end. The harder we work at it the more likely we are to win. I will now outline some of the desirable action[5].

The Principles of Smoking Control: These are now well established[11] and recognised internationally, though governments and countries are very variable in how far they have applied them. The principles can be summarized as follows:

1. A government smoking control program. We must all push as hard as possible for such a program to be established in our own countries and to counter the enormous efforts that the tobacco industry will make to prevent it from being established. Meanwhile it is extremely useful to have a non-governmental organization. This in the first place has to be initiated by doctors, and will aim to influence government, media and the general public.
2. All tobacco promotion of any kind, direct or indirect, should be prohibited[12]. It is very important that breach of the law result in huge fines which may deter even rich companies. A specific government department, and an individual within that department, must be made responsible for ensuring that the law is obeyed and for prosecuting offenders.
3. There should be a progressive increase in cigarette tax[13]. Each increase should be higher than the rate of inflation and higher than any national increase in disposable income. This strategy has been shown to be highly effective in reducing consumption. An increase of 10 percent in tax normally results in about a five percent decrease in consumption. Consequently the government both improves the health of the nation and makes money out of it. This should appeal to politicians and to Finance Ministries.
4. Public places, transportation, workplaces, and of course hospitals and schools should be made progressively smoke-free. This would not only reduce the ill-effects of environmental tobacco smoke but would also create a climate in which smoking becomes increasingly socially unacceptable. For this reason this strategy is bitterly opposed by the tobacco companies.

5. There should be strong and varying government health warnings on all cigarette packets and, pending the abolition of advertising, on all advertisements.
6. There should be intensive and continuous health education both for the general public and, in particular, for opinion leaders, the media, schools, etc. Doctors should take the lead in initiating and supporting this.
7. Sales of tobacco to children should be made illegal. This is mainly an indication of disapproval of society as it can be difficult to implement the law.
8. There should be continuous monitoring in the trends of smoking rates in the general population, in specific occupational groups, and in children. There should be continuous monitoring of mortality and morbidity from smoking-related diseases. The results should be steadily fed back to opinion-markers, decision-makers and the general public. Naturally, the public are much more impressed by figures for their own country.

All these measures must be continuous, comprehensive and frequently varied, in order to capture public interest. It is extremely useful to have a national non-governmental organization which will maintain the pressure on the government and keep the matter before the public.

The Enemy[14] : We have to face up to the fact that, besides the problem of helping people to give up a habit which is so reinforced by nicotine addiction, we have, as I have mentioned above, the strong counter-effect of the tobacco industry attempting to maintain and increase the numbers of children and adults smoking. They do this in many forms, not only by direct advertising, but also by indirect promotion, for instance of sport. By subsidising various public and sporting activities they seek to buy support. They are extremely skilled at lobbying and, by various means, buying powerful friends, for instance by contributing to the funds of political parties. They realise that the problem of environmental tobacco smoke, which persuades the public to establish smoke-free areas, is a major way of creating an anti-smoking climate. Therefore they try to recruit suspect science to throw doubt on the research results. Another more recent method is to threaten with litigation statements from people who are trying to control the epidemic. Of course the industry has vast amounts of money to buy litigation and their opponents have not.

Influences on Individual Behavior: Individual behavior is affected by a large number of factors (Fig. 1).

When children are young, the family influence is very important. Smoking parents are much more likely to have smoking children. As a child grows up the peer group with whom he or she identifies becomes very influential. The school can have a limited effect but it is not likely to be great if there is strong counteracting influence

from the family or the peer group. An individual professional whom the child or adult trusts can certainly have an influence. There is excellent evidence that advice by his/her general practitioner can help individuals to quit smoking. The percentage who do so as a result of such advice may seem disappointing, but if all doctors were doing it all the time, the total who quit would become, nationally, very large.

General health education and the influence of the media form a very important background on which the other factors can act. The counter-effect is from advertising and promotion by the tobacco industry, in some countries suported by the media.

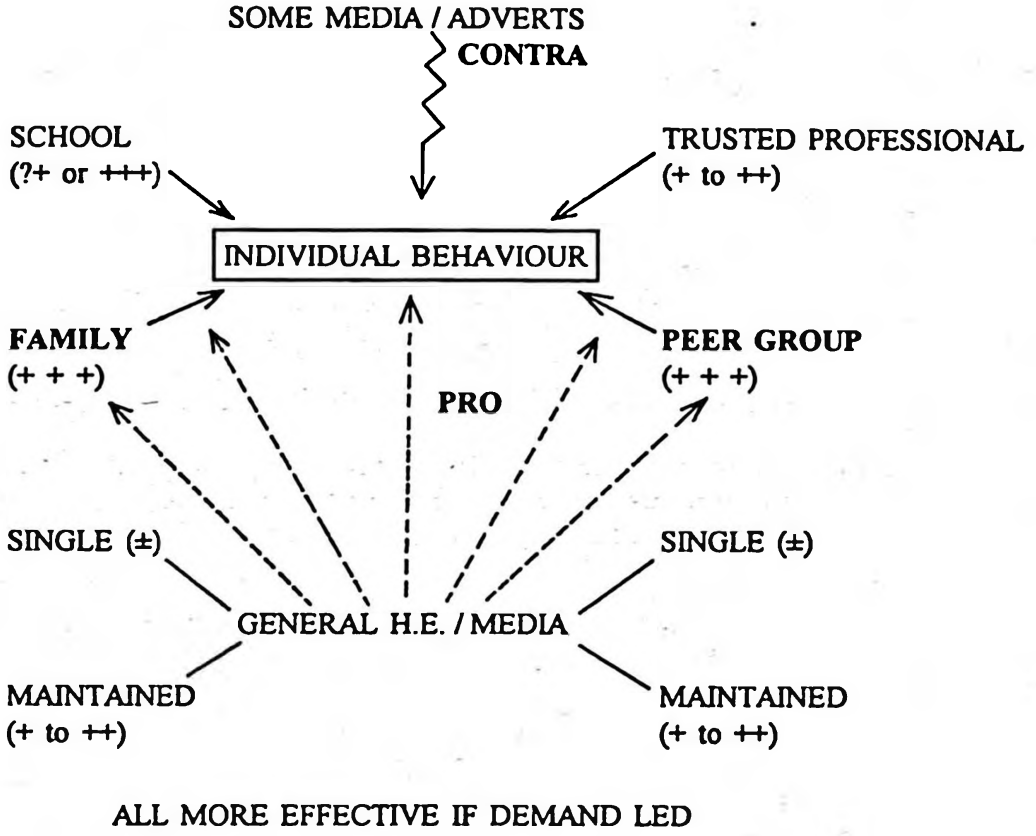

Fig. 1: Factors affecting individual behavior. The number of +s represents the author's assessment of the importance of the factor.

The Process of Achieving National Tobacco Control: Figure 2 shows an outline of this. The first initiative has to be taken by doctors. The doctors can recruit the interests of influential non-doctors. This can lead to a national organization with the objective of establishing effective tobacco control and helping the public to quit. This in turn can influence politicians, the media and decision-makers and so build up the climate of opinion that government may take action along the lines already indicated. Finally smoking becomes no longer socially acceptable.

Success may initially appear to be relatively slight. It will then gradually gather strength as shown symbolically in Figure 3.

The UK As an Example: In the UK we have felt very intense pressure by the medical profession and non-governmental organizations. Unfortunately we have

had rather weak action by successive governments owing to the great power of the tobacco industry. Some of the major multinational companies are based in the UK and have heavily influenced the government.

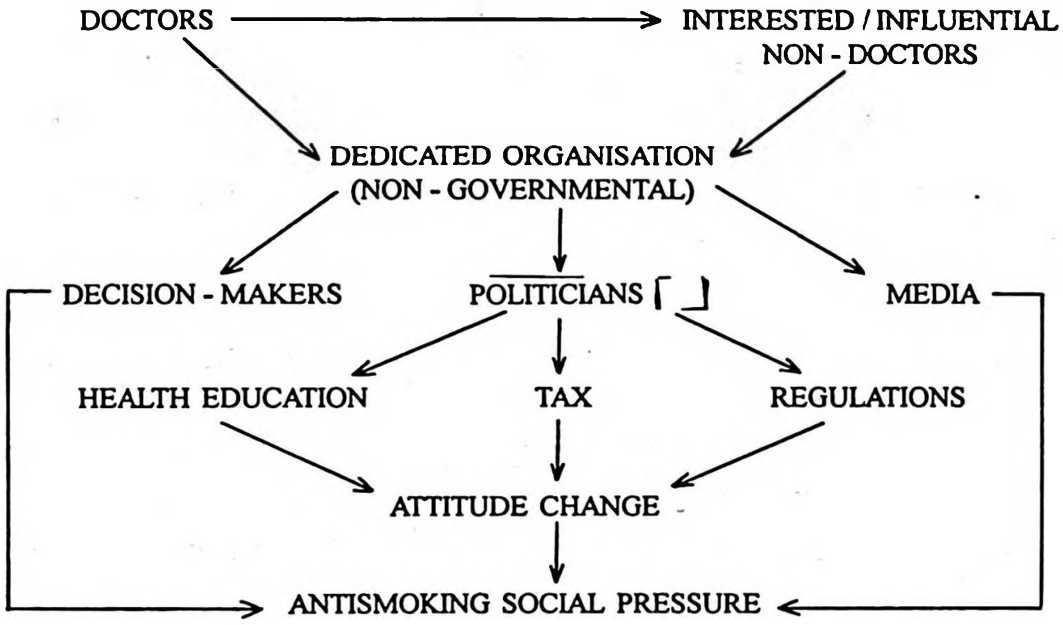

Fig. 2: Achieving National Tobacco Control: The Process. This illustrates the doctors' primary role in recruiting the interest of laymen and the steps leading to ultimate widespread social pressure against smoking.

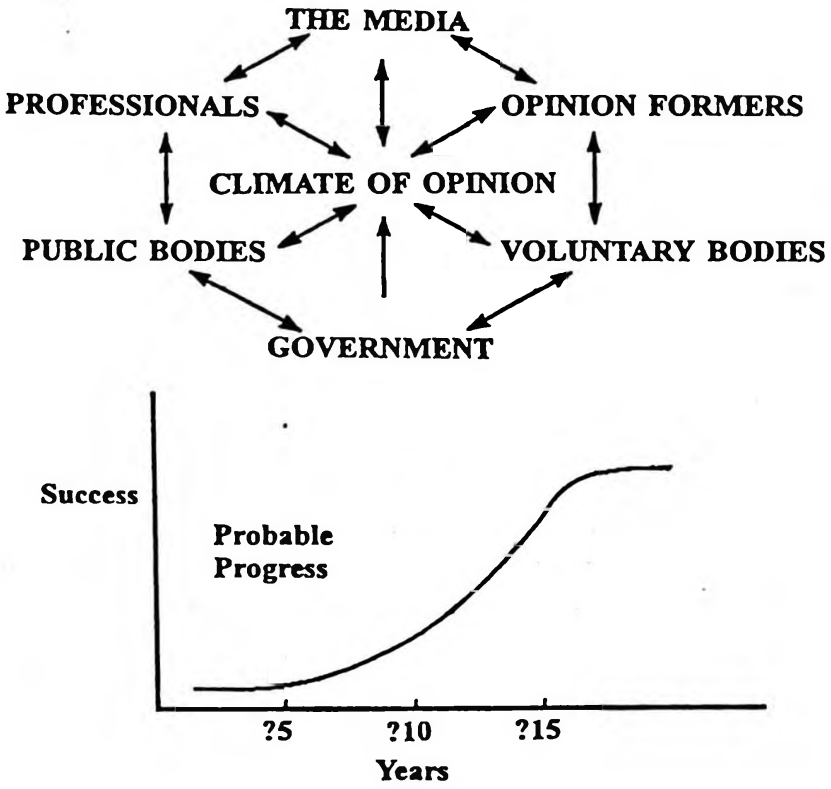

Fig. 3: Factors influencing the development of the climate of opinion. The climate develops slowly at first and then gains momentum.

In Figure 4 I show the UK smoking rates in men, women and male doctors since 1948. (There are no early figures for female doctors). I have placed arrows to show some of the main events which might have affected public opinion and smoking rates.

You will see that the earliest research results[15, 16] had only a slight and relatively temporary effect on male smoking and virtually none on female smoking. They did, however, affect the doctors' rates. These had been higher than the general male rates but soon came down below the male rates. In 1962 the Royal College of Physicians of London, anxious that the results of research had relatively little effect on the public, published a report[17] summarizing the extensive research results to date. Again you will see that this had a very small and temporary effect.

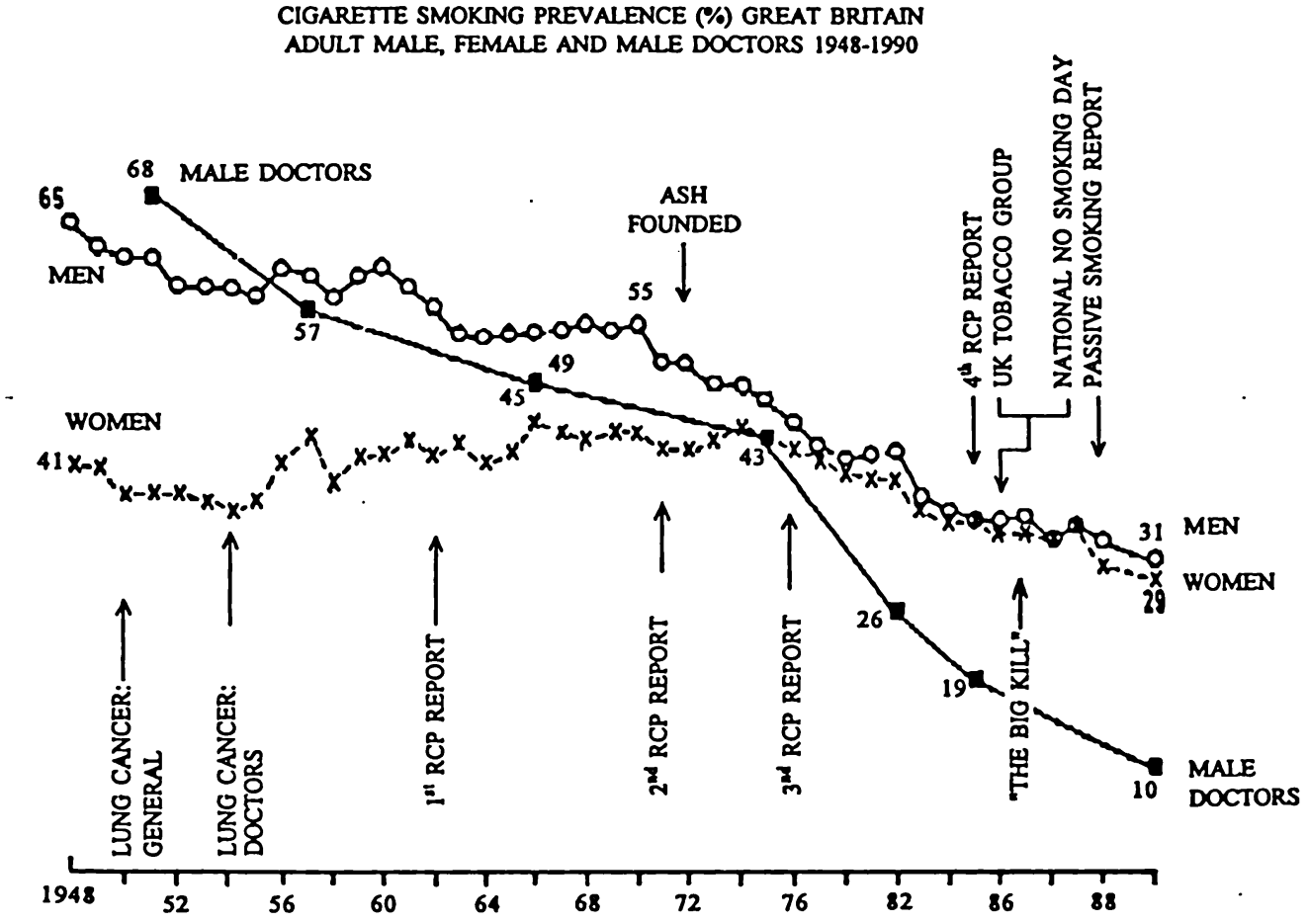

Fig. 4: Cigarette Smoking Prevalence (%) Great Britain: Adult Males and Females, and Male Doctors: 1948-1990. The changes show the relatively small effects of the widely publicized early research and even of the equally publicized comprehensive reports by the Royal College of Physicians of London in 1962 and 1971, but the acceleration of the decline in smoking prevalence (including that of doctors) after the foundation of ASH (Action on Smoking and Health), a non-governmental national body initiated in 1972.

Consequently, when the College's second report in 1971 was published in 1971[18], many of us thought that we must set up a national organization to keep the problem perpetually before the public and the decision-markers. Accordingly the Royal College

of Physicians of London founded Action on Smoking and Health (ASH) in 1972. Although of course there were various other factors, you will note that soon after this the male smoking rate began to reduce more dramatically and the female smoking rate, which had previously changed very little, began to decline as well. It is interesting that the doctors' rate also started to decrease much more dramatically..

Figure 4 shows what a slow business it has been in the UK, although we have over time, achieved a very substantial decrease in smoking rates. I am sure that you in Turkey could do much better. But this depends on extensive efforts, in the first place by doctors, and then by interested laymen, to save your children and future generations from so much of the death and misery which has afflicted my own country in the past and is increasingly afflicting many others. All of us should have an intense feeling of responsibility to do our best to prevent this threatened disaster.

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CHILD AND NEWBORN HEALTH AT THE END OF THE 20th CENTURY*

*Gulamabbas Juma Ebrahim MD***

The last quarter of the 20th century will be remembered as a major turning point in global health. Commencing with the World Conference at Alma-Ata when Primary Health Care came to be defined, there has been unprecedented progress in global health. Historically speaking the underlying principles of Primary Health Care represent the convergence of the Basic Health Strategy advocated by the World Health Organization in the 1960s, and the Basic Needs Approach advocated by the International Labour Organization in the 1970s stressing the importance of food, water, sanitation, shelter and warmth. That was the time when only an estimated 20 percent of people in the developing world were receiving basic health services on a regular basis. Careful analysis of health trends in different countries as well as of small-scale programs helped to identify key elements of Primary Health Care. As nations heeded the call for Health For All by the Year 2000, major milestones have been reached in the global health situation. These milestones were unimaginable in the 1970s. Six killer diseases of children, namely measles, pneumonia, diarrhea, tetanus, whooping cough and malnutrition, jointly responsible for more than eight million deaths annually, have been progressively brought under control. A number of nutritional deficiencies and infective illnesses causing disabilities, such as xerophthalmia, iodine deficiency, trachoma, poliomyelitis, and onchocerciasis, have responded to global action. With the reaching of each milestone, new experience has been gained and lessons learned. These have provided the springboard for the next objective. Already 1995 is earmarked for elimination of neonatal tetanus, and the countdown to the elimination of poliomyelitis by the end of the century has commenced.

Encouraged by the success of the available technologies and methodologies of planning, new targets were set at the World Summit for Children in September 1990 as follows:

1. Reducing the under-five mortality rate by one-third, or to 70 per thousand live births, whichever is the greater reduction.
2. Raising the immunization coverage to 90 percent.

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* From the Department of International Child Health, Institute of Child Health, University of London, London.

** Professor of Pediatrics, Institute of Child Health, University of London.

3. Halving the maternal mortality rates of the 1990s.
4. Halving the 1990 incidence of severe and moderate malnutrition among children less than five years old.
5. Providing safe drinking water and sanitary disposal of excreta for all.
6. Ensuring access by all to basic education.
7. Halving the 1990 rates of adult illiteracy, stressing female literacy.

As nations heeded the call for Primary Health Care, restructuring of health systems and reorientation of policy makers, managers and health workers became necessary. Different countries have met with varying degrees of success. The ability to bring about change in the health sector depends on the political system, the managerial acumen within the country, and the abilty of the training and research institutions to respond to new challenges. The guiding philosophy of Primary Health Care is that equity, availability and social acceptability of health care sets in motion a process in which families and communities are empowered to improve their own health. The emphasis within the health sector, including the training of health workers, has hitherto been predominantly disease-oriented and vertically managed. A great deal of reorientation is needed. Some countries have been more successful than others in achieving the change. An analysis of pathways of improvements in health in countries like China, Sri Lanka, Costa Rica, and the Indian state of Kerala shows that there is a need for innovation on three fronts:

Policy Formulation, requiring: Selection of goals
Identification of strategies of achieving them
Assignment of resources
Assignment of institutional responsibilities

Program administration, requiring: Translating policy into action programs
Establishment of managerial procedures
Development of organizational structures

Service delivery, requiring: Provision of services
Appropriately trained personnel
Implementation of programs

These must be underpinned by political and economic stability, as recent events in Russia prove. There the State Committee for Epidemiological Supervision has reported that the incidence of infectious disease rose by 180 percent in 1994, after a sharper increase of 290 percent in 1993. Life expectancy in Russia is now estimated to be 59 years.

With political will as the engine of change, innovative planning and reorientation of professional training are necessary. Only then can nations arrive at the

mid-decade targets with some degree of assurance for sustainability, and move on to the next phase. The targets for 1995 are:

1. The raising of immunization coverage to at least 80 percent.
2. The elimination of neonatal tetanus.
3. A major reduction in measles cases and deaths.
4. The eradication of polio.
5. The achievement of 80 percent ORT use.
6. Support of breastfeeding through the Baby Friendly Hospital Initiative, and the ending of free or subsidized distribution of formula milk.
7. The virtual elimination of vitamin A deficiency.
8. The universal iodization of salt.
9. The virtual elimination of guinea worm disease.
10. The universal ratification of the Convention on the Rights of the Child.

Based on current information gathered from 61 developing countries, approximately half are likely to reach the mid-decade goals. A clearing of the backlog is essential so as to have a framework in place for progressing to the next stage.

Remarkable advances in the disciplines of genetics, molecular biology, immunology and epidemiology are creating new opportunities for preventing diseases hitherto considered not possible. An example to illustrate this point is that of thalassemia. During the past decade, countries bordering the northern shores of the Mediterranean Sea have experienced a 90 percent drop in births of infants affected by thalassemia major, whereas the situation remains unchanged in countries bordering the southern shores of the Mediterranean. The lesson to be learned is that availability of new technologies can enable us to make inroads to problems hitherto considered intractable. But this would require devising new strategies of Public Health. The old Public Health concentrated quite appropriately on the control of infection and improvement of nutrition. Now the era of a New Public Health is beginning to dawn. Many of the strategies of the New Public Health would need to be firmly grounded as much in social and behavioral sciences, including social epidemiology, as in technological and scientific developments. The pathways of research in genetics, molecular biology and immunology have progressively led towards convergence of these disciplines. One practical outcome has been the development of vaccines. New vaccines (M.M.R.; H.influenzae B; Hepatitis A; Hepatitis B; new oral and injectable vaccines against typhoid fever; rota virus; cholera and malaria) are already either in common use or undergoing field trials. Several more are in the pipeline. At the same time a host of new diagnostic tools are becoming increasingly available

to the health profession. Nations who have successfully cleared the backlog will be better placed to utilize these new developments. The obvious reason is that success in clearing the backlog is a measure not only of political will but also of efficiency and responsiveness in the health sector. Some countries, notably China, having achieved remarkable change in the health situation, are already planning what they call the Second Health Revolution wherein diseases like cancer, hypertension, coronary artery disease, cerebrovascular disease and chronic lung disease would be targeted for prevention.

With the Child Survival Revolution firmly in place and the Safe Motherhood Initiative gaining ground, the time has come to target the health of the newborn. There are two compelling reasons for doing so. As in the case of the Child Survival Revolution, a handful of low-cost technologies can be identified to ensure the smooth transition of the newborn to extrauterine life. Secondly, epidemiological research indicates that the fetal and neonatal periods, as well as infancy and early childhood, are likely to become the focus of several strategies of the New Public Health. Evidence of physiological programming through breastfeeding, hormonal signals operating during the early formative periods of life, and of external stimuli is sufficiently strong to provide the rationale for health action. Low body weight, head circumference and ponderal index at birth, and low weight at one year have been associated with increased risk of cardiovascular disease in adulthood. Small size at birth and up to one year has also been associated with higher blood pressure and adverse changes in plasma concentration of a number of substances, including glucose, insulin, fibrinogen, Factor VII and apolipoprotein B all related directly or indirectly with vascular physiology. Poor fetal nutrition, perhaps resulting from poor maternal nutrition, adversely programs the individual for cardiovascular disease, hypertension and diabetes in adult life. The strength of evidence about folic acid deficiency during pregnancy resulting in neural tube defects in the fetus is sufficient for countries to implement programs of supplementation during the antenatal period. The importance of breastfeeding for developmental maturation of the newborn's body systems, including cognitive development and metabolic programming for later life, is now well recognized. These observations have led to global programs for the promotion of breastfeeding. With regard to early childhood experiences it has been shown that negative emotional experiences in early life operate in the long term by inducing disruptive behavior. Such behavior, in turn, increases the frequency of stressful life events, thereby predisposing the individual to psychopathology in adult life.

While we contemplate the new possibilities, we should also remind ourselves of the present trend for evidence-based medicine, including in Public Health. As costs of medical care have escalated in country after country, big purchasers such as governments, health insurers and employers of large workforces are

beginning to turn away from curative care. They are increasingly demanding best buys and value for money in preventive/promotive care.

There are also emerging new problems. The rise in poverty, urban decay and the associated problems of single-parent families, teenage pregnancy, street children, substance abuse and violence create a social situation in the context of which new disease problems, such as HIV infection, would need to be tackled. These call for programs at the grass roots level in which social epidemiology, behavioral science and the New Public Health blend together.

Are we creating a new breed of community health worker capable of carrying the message of health and the fruits of scientific progress to those who need them most? Are we providing such health workers with simple and scientifically sound technologies for applying within the home and the community?

To what extent are our frontline workers being equipped to create a healthy world for the newborn to come into in the 21st century?

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TETRAHYDROBIOPTERIN AND INHERITED HYPERPHENYLALANINEMIAS*

*Nenad Blau PhD***, *Beat Thöny PhD****; *Marco Spada MD*****
*Alberto Ponzone MD******

SUMMARY: Blau N, Thöny B, Spada M, Ponzone A. (Division of Clinical Chemistry, Department of Pediatrics, University of Zürich, Zürich, Switzerland, and Department of Pediatrics, University of Turin, Turin, Italy, and Facolla di Magistero, University of Messina, Messina, Italy). Tetrahydrobiopterin and inherited hyperphenylalaninemias. Turk J Pediatr 1996; 38: 19-35.

Tetrahydrobiopterin deficiency, a variant of hyperphenylalaninemia, may be caused by deficiency of one of the following enzymes: guanosine triphosphate cyclohydrolase 1, 6-pyruvoyltetrahydropterin synthase, dihydropteridin reductase and pterin-4a-carbinolamine dehydratase. The first two enzymes are involved in the biosynthesis of tetrahydrobiopterin, the last two in its regeneration. Although these diseases are rare, early detection by selective screening is essential for the treatment and outcome. Tetrahydrobiopterin deficiencies are very heterogenous ranging from mild forms requiring only marginal if any treatment to severe forms which are in some cases very difficult to treat. All variants of tetrahydrobiopterin deficiency can be differentiated from the classical phenylketonuria (PKU) by measurement of pterin metabolites in patients' urine, tetrahydrobiopterin loading test, and by dihydropteridine reductase activity in erythrocytes from the Guthrie card. *Key words: hyperphenylalaninemia, phenylketonuria, tetrahydrobiopterin, biopterin, neopterin, phenylalanine, neonatal screening, genetics.*

Function of Tetrahydrobiopterin

The best established function of tetrahydrobiopterin (BH_4) in man is as the natural cofactor for phenylalanine-4-hydroxylase (PAH), tyrosine-3-hydroxylase, and tryptophan-5-hydroxylase; the latter two are key enzymes in the biosynthesis of biogenic amines[1]. In addition to the hydroxylation of aromatic amino acids, BH_4 serves as the cofactor for nitric oxide synthase[2] and glyceryl-ether monoxygenase[3] (Fig. 1).

* From the Division of Clinical Chemistry, Department of Pediatrics, University of Zürich, Zürich, and from the Department of Pediatrics, University of Turin, Turin, and from Facolla di Magistero, University of Messina, Messina.

** Biochemist, Department of Pediatrics, University of Zürich.

*** Molecular Biologist, Department of Pediatrics, University of Zürich.

**** Pediatrician, Department of Pediatrics, University of Turin.

***** Pediatrician, Department of Pediatrics, Facolla di Magistero, University of Messina.

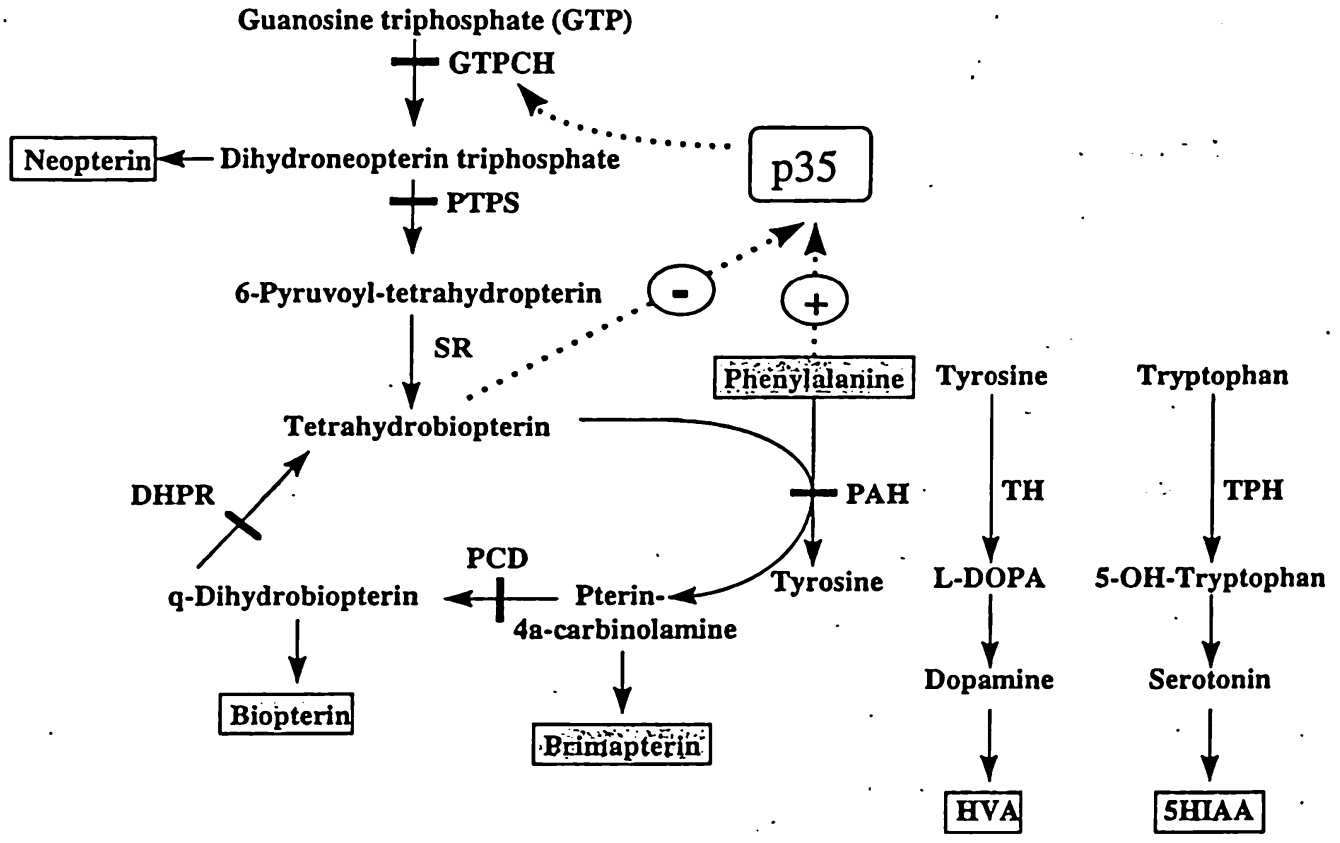

Fig. 1: Biosynthesis and regeneration of tetrahydrobiopterin including hydroxylation of aromatic amino acids. Pathological metabolites used as specific markers in the differential diagnosis are marked in squares.

GTPCH	= GTP cyclohydrolase I	PTPS	= 6-pyruvoyl-tetrahydropterin synthase
SR	= sepiapterin reductase	PCD	= pterin-4a-carbinolamine dehydratase
DHPR	= dihydropteridine reductase	PAH	= phenylalanine-4-hydroxylase
TH	= tyrosine-3-hydroxylase	TPH	= tryptophan-5-hydroxylase
L-DOPA	= 3,4-dihydroxyphenylalanine	HVA	= homovanillic acid
5HIAA	= 5-hydroxyindoleacetic acid	p35	= GTPCH stimulating protein

The function of these reactions derives from the ability of BH_4 to react with molecular oxygen to form an active oxygen intermediate that can hydroxylate substrates. In the hydroxylation process, the co-enzyme loses two electrons and is regenerated in vivo in an NADH-dependent reaction. Although BH_4 was found to be absolutely essential for nitric oxide synthase activity, the exact function in different forms of the enzyme and the mechanism of action are as yet unclear. Furthermore, it has been demonstrated that BH_4 increases the proliferation rate of erythroid cells[4] and that it is active as a dopamine-releasing factor in rat striatum by using an in vivo dialysis technique[5].

Metabolism of Tetrahydrobiopterin

BH_4 is synthesized from guanosine triphosphate (GTP) in at least four enzymatic steps by the action of three different enzymes (Fig. 1)[6-9]. GTP cyclohydrolase

I (GTPCH), the first enzyme in BH_4 biosynthesis, catalyzes the formation of 7,8-dihydroneopterin triphosphate from GTP in a single reaction step[10]. GTPCH is subject to feedback inhibition by BH_4. Inhibition occurs through a BH_4-dependent complex formation between a newly discovered p35 protein and GTPCH[11]. Furthermore, the inhibition is specifically reversed by phenylalanine. These may explain the high neopterin and biopterin contents observed in patients with hyperphenylalaninemia (HPA)[12].

In the following step, the 6-pyruvoyl-tetrahydropterin synthase (PTPS) catalyzes the conversion of 7,8-dihydroneopterin triphosphate to 6-pyruvoyl-tetrahydropterin[13].This conversion is magnesium-and zinc-dependent and involves the elimination of triphosphate and an intermolecular redox rearrangement reaction[14]. Whereas GTPCH is found to be highly regulated by the p35 protein, for PTPS no such regulatory processes are described. Nevertheless, PTPS needs post-translational modification(s), i.e., phosphorylation, in order to be fully active in vivo[15]. Furthermore, it has been suggested that PTPS is the rate-limiting enzyme for BH_4 biosynthesis, at least in the human liver[16].

Sepiapterin reductase (SR) has been shown to be an NADPH oxidoreductase required for the final two-step reduction of the diketo intermediate 6-pyruvoyl-tetrahydropterin to BH_4[17].

During the enzymatic hydroxylation of aromatic amino acids, molecular oxygen is consumed and tetrahydrobiopterin is peroxidated and oxidized. The pterin intermediate is subsequently reduced back to BH_4 by two enzymes and a reduced pyridine nucleotide (NADH) in a complex recycling reaction (Fig. 1). Molecular oxygen is first bound to BH_4 to form an unstable 4a-peroxy-tetrahydrobiopterin. The monooxygenation of aromatic amino acids is thus concomitant with oxidation of BH_4 to 4a-hydroxy-tetrahydrobiopterin (pterin-4a-carbinolamine)[18]. Pterin-4a-carbinolamine is subsequently dehydrated to quinonoid-dihydrobiopterin (q-dihydrobiopterin) and water by the specific and highly efficient pterin-4a-carbinolamine dehydratase (PCD)[19, 20]. The PCD was originally detected as a contaminant in a preparation of the rat PAH as a consequence of its ability to stimulate the BH_4-dependent hydroxylation of phenylalanine[21]. PCD activity was also shown to be present in human liver, and its absence is concomitant with the formation of 7-substituted pterins[22]. Unexpectedly, the primary structure of PCD is identical with a protein of the cell nucleus, named dimerization cofactor of hepatocyte nuclear factor 1a (DCoH), reported to have a general transcriptional function[23-25]. However, the dual function of regulation of PAH activity and transcription activation in a single protein is unprecedented.

In the last step of BH_4 recycling, the q-dihydrobiopterin is reduced back to BH_4 by the NADH-dependent dihydropteridine reductase (DHPR). There is no

evidence that DHPR has regulatory properties; however, it has been shown that a number of drugs can inhibit the enzyme's activity, both in vivo and in vitro. For instance, methotrexate, an antineoplastic drug commonly used in the treatment of cancer, can significantly inhibit DHPR activity[26].

Tetrahydrobiopterin Deficiency

The first patients with BH_4 deficiency were identified in 1969 by Tada et al.[27] Two siblings with mild HPA were, at that time, described as "a genetic variant of phenylketonuria" (PKU), but later were characterized as DHPR-deficient[28]. In 1974 in London, Smith et al.[29] described three children with "PKU" who had an unusual clinical course. Despite early diagnosis and treatment with a low-phenylalanine diet, these patients developed progressive neurological disease and died. Independently, Bartholomé[30] in Heidelberg reported a similar case of "atypical" HPA unresponsive to dietary treatment. The atypical course, high tolerance for phenylalanine and normal PAH activity in liver biopsy in Bartholomé's patient, led to the speculation that this syndrome was a new form of HPA, probably due to a defect in the metabolism of BH_4. Smith et al.[29] reasoned that a defect in the metabolism of BH_4 in brain tissue would also result in defective turnover of the neurotransmitters L-DOPA, noradrenaline, and serotonin. In the following years a number of cases of BH_4 deficiency were described, and it was suggested that all these patients suffered from a defect in BH_4 metabolism[31-39]. Because all untreated patients show severe cerebral deterioration and most of them die at an early age, it was suggested that this clinical syndrome should be called "malignant" HPA[40, 41].

Based on the speculation that pterins might be used in the treatment of PKU, Smith et al.[31] proposed that patients with BH_4 deficiency might benefit from substitution with reduced pterins. Indeed, Danks et al.[36] showed that intravenous administration of synthetic BH_4 decreases the serum phenylalanine levels and, therefore, can function as a cofactor subsituting for hepatic PAH in vivo. Meanwhile, therapy with L-DOPA, carbidopa, and 5-hydroxytryptophan alone or in combination with BH_4, was shown to be beneficial for patients with various forms of BH_4 deficiency[42-49].

Because BH_4 deficiency may cause a severe disease but is treatable, it became necessary to develop selective screening tests for detection early in infancy. Every newborn with even slight but persistent HPA should be tested for a BH_4 deficiency. Such tests have been introduced in many developed countries, but even today older children are invariably detected because of the appearance of clinical symptoms, such as hypotonia of the trunk, hypertonia of the extremities, and often myoclonic seizures, which are unresponsive to a low-phenylalanine diet. According to the literature the frequency of BH_4 deficiency is estimated to

be one to two percent among cases with HPA[50-52], although in some countries, such as Turkey and Saudi Arabia, because of consanguinity the incidence is even higher.

Nomenclature of Tetrahydrobiopterin Deficiency

The BH_4 deficiencies are a heterogeneous group of diseases, and different phenotypes, ranging from very mild to severe forms, define the variants. The terms severe/general or mild/peripheral/partial can be used according to the actual need for treatment[51]. Accordingly the following nomenclature applies (Table I). Older terms such as "atypical PKU" (non-PKU hyperphenylalaninemia) or "malignant PKU" should be avoided.

Table I: Overview of Tetrahydrobiopterin Deficiencies and Treatment

Defect	Phenotype	Neonatal HPA Phe (µmol/L)	BH_4 Loading (20 mg/kg)	Residual Enzyme Activity (%)	Neurotransmitters and/or BH_4 Therapy
GTPCH deficiency	severe	120-1200	+	< 1*	+
PTPS deficiency	severe	250-2500	+	0-20**	+
	mild	240-2200	+	8-31**	–
DHPR deficiency	severe	180-2500	+•	< 1***	+
	mild	280-600	+	< 5***	–
PCD	transient	180-1200	+	?	–

* liver. ** erythrocytes. *** fibroblasts.
• at least two patients with "non-responder" phenotype are documented.

Selective Screening and Ultimate Diagnosis

Because BH_4 deficiencies are a group of diseases that can be detected but not identified through neonatal mass screening for HPA, selective screening for a BH_4 deficiency is essential in every newborn with even slightly elevated phenylalanine levels[53, 54]. Screening for a BH_4 deficiency should be done in all newborns with plasma phenylalanine levels higher than 120 µmol/L, as well as in older children with neurological signs and symptoms. The following tests are recommended:

1. Analysis of pterins in urine (see Appendix).
2. Measurement of DHPR activity in blood from Guthrie card (see Appendix).
3. Loading test with BH_4 (see Appendix).

The first two tests are essential and allow differentiation between all BH_4 defects. With some limitations, the BH_4 loading test is an additional, useful diagnostic tool for rapid differentiation between calissical PKU and the BH_4 variants. A diagnostic flow-chart is shown in Figure 2.

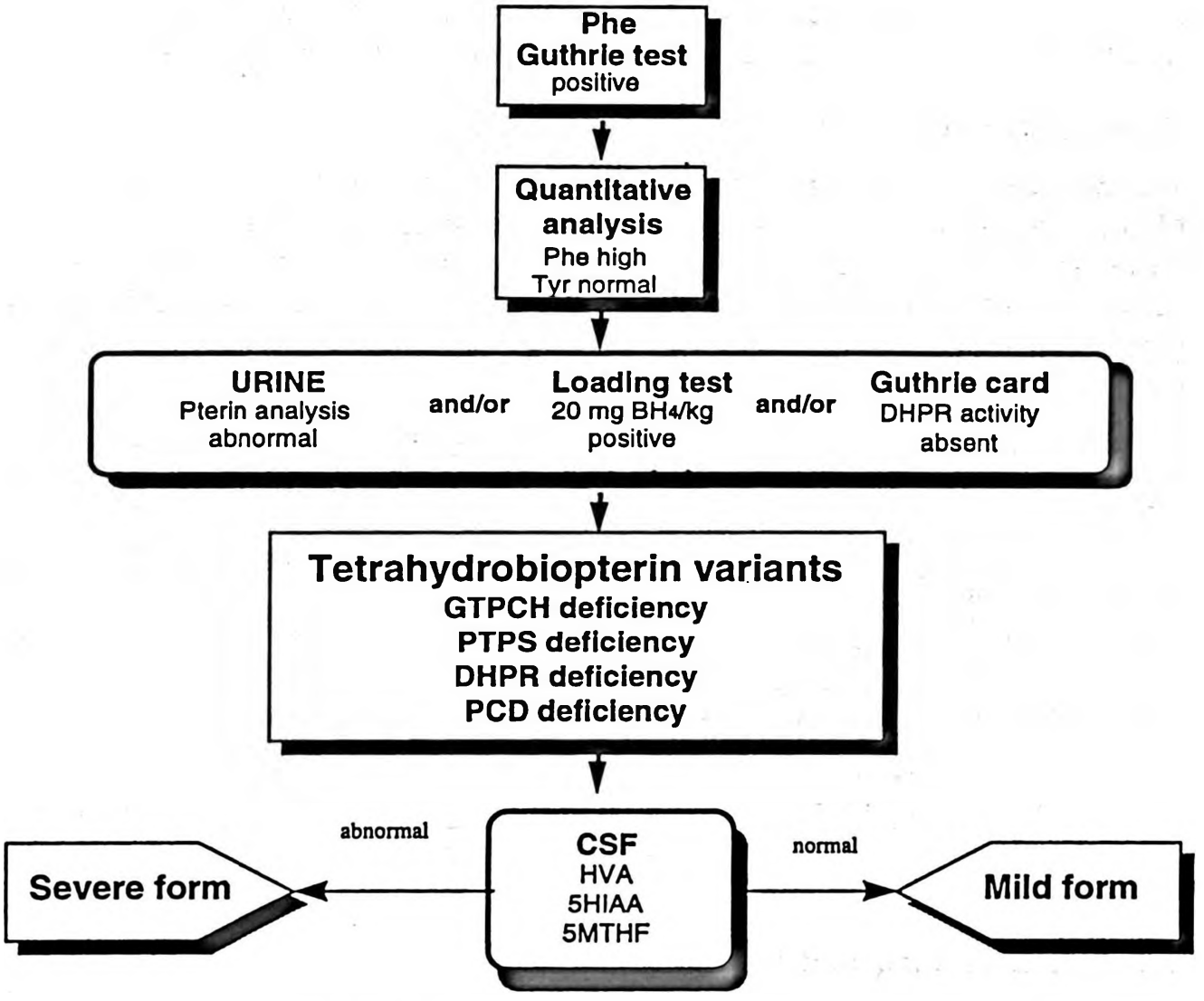

Fig. 2: Diagnostic flow-chart for the differentiation of hyperphenylalaninemias.

Phe = phenylalanine
Tyr = tyrosine
GTPCH = GTP cyclohydrolase I
PTPS = 6-pyruvoyl-tetrahydropterin synthase
PCD = pterin-4a-carbinolamine dehydratase
DHPR = dihydropteridine reductase
HVA = homovanillic acid
5HIAA = 5-hydroxyindoleacetic acid
5MTHF = 5-methyltetrahydrofolic acid

Analysis of Pterins

Liquid urinary samples or even better a random urine specimen dried on filter paper can be used[55]. Reduced urinary pterins are extremely unstable and are affected by daylight, temperature and storage time. The recovery of pterins in urine dried on filter paper and stored at room temperature for one and two weeks showed good correlation with standard methods. A significant advantage of this method is that the samples can be mailed unfrozen in an envelope, speeding delivery and minimizing costs.

Typical urinary pterin profiles are as follows: in GTPCH deficiency, neopterin and biopterin are very low; in PTPS deficiency, neopterin and monapterin (isomer of neopterin) are very high and there are only traces of biopterin; in DHPR deficiency, neopterin is normal or slightly increased and biopterin is very high; and in PCD deficiency, neopterin is initially high, biopterin is in the subnormal range and primapterin (7-substituted biopterin) is present. Patients with classical PKU excrete generally more neopterin and biopterin in urine compared with the normal controls.

By two-dimensional plotting of total biopterin versus percentage of biopterin, of the sum of neopterin plus biopterin, variants of HPA can be separated (Fig. 3).

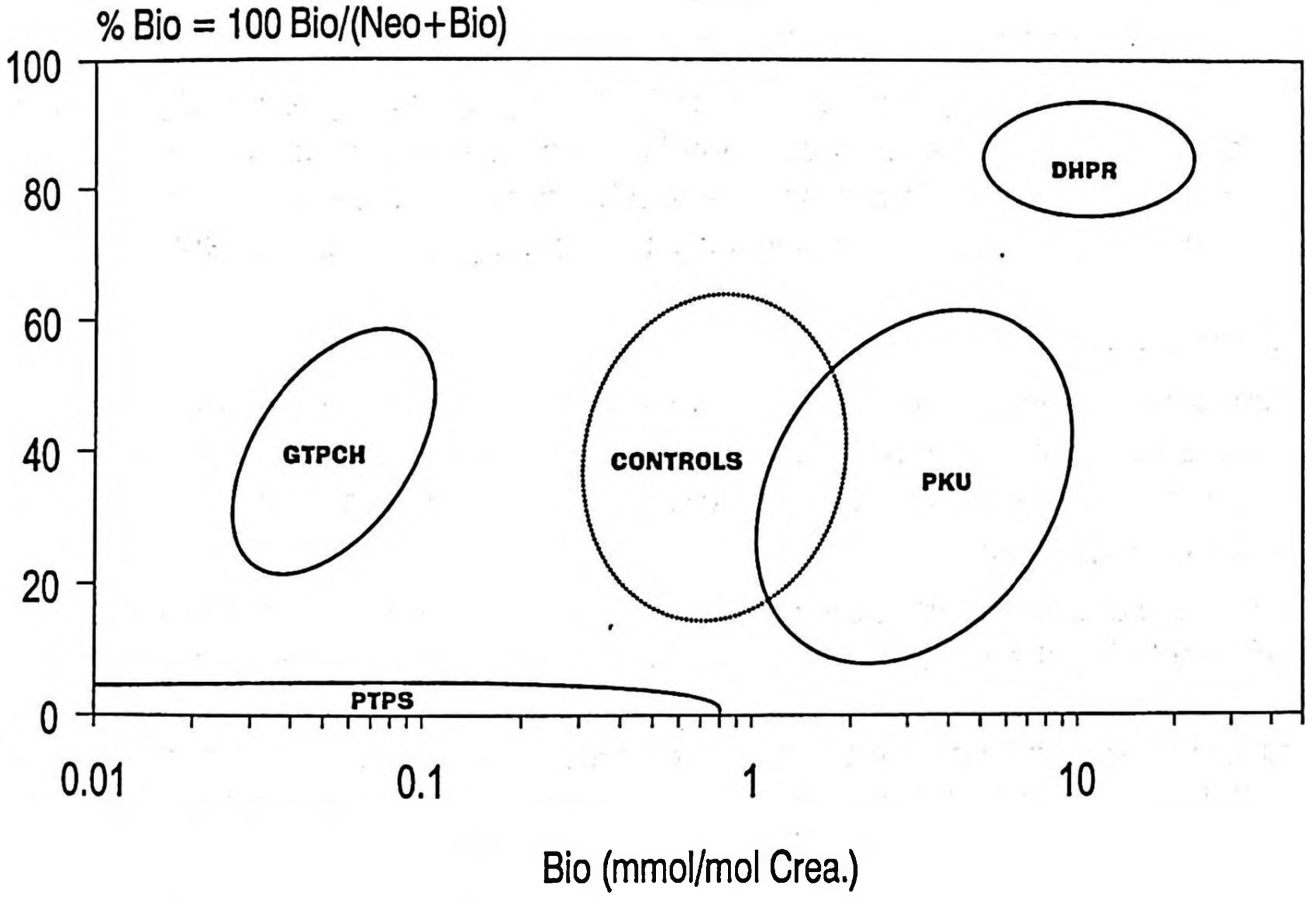

Fig. 3: Two-dimensional semilogarithmic plotting of total urinary biopterin and percentage of biopterin. Percentage of biopterin is calculated from the sum of neopterin and biopterin.

Loading Tests

Two types of loading tests have been used in the differential diagnosis of BH_4 deficiencies:

1. A simple oral BH_4 load
2. A combined phenylalanine and BH_4 load

Historically, the first method tried[36] which was predicted as the most convenient to screen selectively among HPAs, exploited the lowering of plasma phenylalanine in BH_4-deficient patients after the administration of exogenous BH_4. Intravenous

loading with 2 mg/kg BH_4 was originally proposed by Danks et al.[37] With the increased purity and availability of this synthesized cofactor (BH_4), an oral loading test (2.5 mg/kg bw) was introduced by Niederwieser et al.[56] and was standardized at a dose of 7.5 mg/kg by the same group[48]. This very simple test discriminated between patients with PAH and BH_4 deficiencies. However, it soon became obvious that some DHPR-deficient patients could be misdiagnosed, in as much as their serum phenylalanine levels were not lowered by BH_4[57], thus introducing an unacceptable limitation if this was the sole test performed. The observation that BH_4 nonresponsiveness in DHPR deficiency correlates with the presence of a mutant enzyme[58] and that it can be overcome by increasing the dose (20 mg/kg bw) of the administered synthetic cofactor, led to a new standard protocol for BH_4 loading.

Phenylalanine (100 mg/kg bw) plus BH_4 (20 mg/kg bw) given orally enables selective screening of all BH_4 deficiencies when pterin analysis is not available or when a clear diagnosis has not previously been made[59]. In this simplest form, this test can be interpreted using only four blood spots from a Guthrie card.

Additional Tests

Ultimate diagnosis can be established by enzymatic studies and by measurement of the cerebrospinal fluid (CSF) concentrations of the major dopamine and serotonin catabolites, homovanillic acid (HVA) and 5-hydroxyindole acetic acid (5-HIAA), respectively.

PTPS[60] and DHPR[61] activities are both expressed in erythrocytes and skin fibroblasts, thus simplifying the patients' investigations. GTPCH activity is measurable in the liver[62] and in cytokine-stimulated mononuclear cells[63] or fibroblasts[64, 65], while PCD activity is measurable only in the liver[19]. As reported below, the human genes and/or cDNAs coding for all these enzymes have been cloned, and mutation analysis is in progress to establish a genotype-phenotype correlation.

The measurement of CSF neurotransmitter metabolites is of capital importance for clinical and treatment follow-up, as it allows separation of typical from atypical cases of BH_4 deficiency (the latter are phenotypically defined by the absence of clinical signs and symptoms and do not need any treatment for biogenic amine deficiency).

Treatment and Prognosis

With the exception of cases with PCD deficiency, which is generally a benign and transitory form of HPA[66, 67], untreated patients with typical BH_4 deficiency show a virtually similar picture of progressive neurological deterioration, regardless of the different enzyme defects[68, 69]. The median age of onset of the clinical presentations is between four and five months[68]; however, abnormal signs (microcephaly, poor suckling, hypotonia) may be present since birth, particularly

in PTPS deficiency, suggesting that in utero damage may occur[70]. Within a few months, patients develop a typical neurological syndrome characterized by disturbances of tone and posture (truncal hypotonia with limb hypertonia), tremors, hypokinesis, drowsiness, irritability, swallowing difficulties, abnormal movements, oculogiric crises, grand mal or myoclonic convulsions, and recurrent episodes of hyperthermia without infections. These symptoms are due to the combined amine deficiency (Table II), fluctuate diurnally in their intensity, and can even be completely nullified by treatment. With time, untreated patients develop progressive microcephaly associated with electroencephalogram (EEG) paroxysmal activity as well as brain atrophy on computerized tomography scan or magnetic resonance imaging. If HPA has not been treated soon after birth[71], treatment becomes ineffective and death occurs in infancy or childhood. In addition to the above symptoms, patients suffering from DHPR deficiency may develop long-term signs associated with perivascular calcifications located in the basal ganglia and in the areas of the white and gray matter[73]. These changes are irreversible and are thought to occur as a result of inhibition of folate metabolism when folinic acid is not substituted[73, 74].

Table II: Symptoms Related to Specific Biogenic Amine Deficiency

Dopamine	Serotonin	Noradrenaline
Immobility	Depression	Axial hypotonia
Parkinsonism	Altered thermogenesis	Cerebellar symptoms
Sleepiness	Insominia	
Dystonia		
Eye rolling		
Swallowing difficulties		

The prognosis of severity in BH_4 deficiency is closely related to the degree of HPA and to impaired biogenic amine production. Therefore a combination of therapies to correct this metabolic clutter must be applied promptly after diagnosis. Control of HPA can be achieved either by a phenylalanine-restricted diet or by administration of synthetic BH_4. The dietary tolerance to phenylalanine is higher in BH_4 deficiency (300-700 mg/d) than in classical phenylketonuria, but normal serum phenylalanine levels should be attained to avoid interference with neurotransmitter metabolism[75]. The diet can be calculated following the lines used in phenylketonuria, also supplementing tyrosine. The administration of synthetic BH_4 is always effective in the control of HPA. A single, small daily dose (1-5 mg/kg) is sufficient in synthesis defects, while larger and fractionated daily doses (20 mg/kg, given in 3-4 doses) are necessary in some DHPR-deficient patients[76]. It should be noted, however, that the dietary phenylalanine tolerance increases markedly with age in these patients (Ponzone A, Spada M, personal communication).

Despite substantial amounts of peripherally administered BH_4 found in CSF[77, 78], only a few patients respond at the central level to BH_4 monotherapy by normalizing their neurotransmitter production[44, 45, 76, 79]. Most patients need neurotransmitter substitutive therapy[80-83]. This can be realized by administering the precursors L-dopa and 5-hydroxytryptophan in conjunction with carbidopa, an inhibitor of peripheral aromatic amino acid decarboxylase. Daily doses and the number of administrations must individually adjusted according to the patient's age and requirements (Table III).

Table III: Therapy of Tetrahydrobiopterin Deficiencies

Therapy	Age	Doses / day	PTPS / GTPCH Deficiency	DHPR Deficiency
		Combined Therapy		
Phenylalanine-low diet or	initially	–	no	yes no
BH_4 (mg/kg/d)	initially	1	1-5	no 20
L-DOPA (mg/kg/d) + 10%	initially	3-4	1-2	1-2
Carbidopa	< 2y	3-4	5	5
	> 2y	3-4	8-10	8-10
5-Hydroxytryptophan (mg/kg/d)	initially	3-4	1-2	1-2
	< 2y	3-4	5	5
	> 2y	3-4	6-8	6-8
Folinic acid (mg/d)	initially	1	no	10-20
		BH_4 Monotherapy		
BH_4 (mg/kg/d)	initially	1-2	5-20	no 20

Monitoring of treatment can be implemented either clinically, by evaluating the minimal dose effective in relieving cardinal symptoms, or biochemically, by periodically measuring the CSF concentration of HVA and 5-HIAA[71]. Unfortunately, when higher doses of neurotransmitter precursors are necessary, patients may show prominent overdose effects or on-off phenomena[84]. Good results have recently been obtained in similar cases with the concurrent administration of L-deprenyl, a selective monoamine oxidase (MAO) B inhibitor, allowing dosage reduction of administered precursors by curtailing their catabolism[85].

Folinic acid administration (10-20 mg per day) is mandatory only in DHPR deficiency to avoid folate depletion.

The clinical outcome of BH_4 deficiency depends largely on early treatment intervention and compliance. Fetal damage and delay in treating HPA, with subsequent irreversible damage, worsen the prognosis.

Incidence and Genetics

All variants of BH_4 deficiencies have an autosomal recessive trait. The frequency of all BH_4 deficiencies is uncertain, but, assuming they represent altogether about

one to two percent of PKU patients, the combined frequency of BH_4 deficiencies is approximately 1:10^6 live births. Data from newborn and selective screening programs reveal regional (demographic) variations in the frequency of BH_4 deficiencies[52]. In the Piemonte region as well as in southern parts of Italy, 10 percent of all patients with HPA are accounted for by BH_4 deficiencies (Ponzone A, personal communication). In Turkey, the incidence is even higher (15%)[86]. In Taiwan, it is percent 19 percent[87], and Saudi Arabia has the highest incidence (66%)[88, 89].

GTPCH, PTPS, PCD, and DHPR are each encoded by single genes, and the corresponding loci are mapped to chromosomes 14q21q-q22, 11q22.3-q23.3, 10q22, and 4p15.3, respectively[90-93]. Phenotypically, BH_4 deficiencies are a very heterogeneous group of disorders. Cloning of the wild-type genes and/or corresponding cDNAs now enables characterization of mutations on the nucleotide level, which extends the initially limited studies by enzymatic assays of cultured primary cells or patients' lymphocytes. So far, only a limited number of patients with GTPCH deficiency[16, 94], PTPS deficiency[15, 95-98], DHPR deficiency[99-101], and PCD deficiency[20, 102] have been investigated for DNA mutations that result in RNA splicing defects or in abberrant mutant proteins. Studies of the consequences on the enzymatic activity and/or stability of mutations resulting in amino acid substitutions, deletions or insertions, and truncations were performed by recombinant expression of the corresponding mutant proteins. These combined analyses will help to understand the different clinical phenotypes of BH_4 deficiencies.

Appendix

Collection of Liquid Urine Specimens: Pipette 5 ml of fresh random urine into a centrifugation vial and adjust pH to 1.0-1.5 with 6M HCl, Add 100 mg of manganese dioxide (MnO_2, No: 5957, Merck, Darmstadt, Germany) and shake for 5 min at room temperature. Centrifuge for 10 min at 4000 rpm. Immediately transfer 1 ml of the clear supernatant into a vial for shipment. Wrap the vial in aluminum foil to protect from light.

Collection of Dried Urine Specimens: Fresh random urine was processed as described for liquid specimen. Filter paper strips (3x5 cm, filter paper backing 165-0921, Bio-Rad, Richmond, USA) were dipped into the clear supernatant of the oxidized urine up to 1 cm below the upper edge. Excess urine was wiped off and the filter paper was left to dry at room temperature in dim light. The filter strip was then covered with aluminum foil and sent to the laboratory in an envelope by express mail.

Loading Test with BH_4 (20 mg/kg bw): A simple oral BH_4 loading test was performed at least 30 min before the meal. BH_4 tablets (No: 2501.00.00, Milupa AG, Friedrichsdorf, Germany, or Dr. Schircks Lab., Jona, Switzerland, or Suntory

Pharmaceuticals, Tokyo, Japan) were dissolved in orange juice or water (ca. 10 ml per 10 mg BH_4) and administered immediately at a dose of 20 mg/kg body weight. Blood for the analysis of phenylalanine and tyrosine was collected before, and 4 and 8 hours after administration.

Combined Loading Test with Phenylalanine (Phe) (100 mg/kg bw) and BH_4 (20 mg/kg bw): Tablets of synthetic cofactor (20 mg/kg body weight) were dissolved as described above and administered 3 hours after the Phe load (100 mg/kg body weight). Blood was collected before, and 3, 7, and 11 hours after Phe administration. Store at -20 °C.

Blood Collection for DHPR Activity: Collect 2-4 drops of blood on a Guthrie card. Protect the card from humidity.

Collection of CSF Specimen: Discard the first 0.5 ml of the CSF and collect the next 1.0 ml in an EDTA tube. Keep immediately frozen at -20 °C.

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SURFACTANT AND RESPIRATORY DISTRESS SYNDROME*

*Anthony David Milner MD***

SUMMARY: Milner AD. (Department of Neonatology, St. Thomas Hospital, London, England). Surfactant and respiratory distress syndrome. Turk J Pediatr 1996; 38: 37-43.

Since the late 1950s it has been known that the cause of respiratory distress syndrome (RDS) is surfactant deficiency, especially in preterm infants. But surfactant protein B deficiency may cause RDS in term infants as well. Administration of natural surfactant produce is well known to a rapid improvement in oxygenation within 15 to 20 minutes. The effect of synthetic surfactant is less dramatic. Although randomized controlled trials have been done, the majority have been relatively small. Studies on the role of natural surfactant given to infants with established RDS (rescue therapy) have shown a reduction in the incidence of neonatal death and pneumothorax of 40% and 65%, respectively, compared to untreated infants. However, natural surfactant provides no apparent benefits in terms of the incidence of intraventricular hemorrhage (IVH), patent ductus arteriosus (PDA) or bronchopulmonary dysplasia (BPD). The results of synthetic surfactant given as rescue therapy have shown a similar effect with a 40% reduction in mortality and a 48% reduction in pneumothorax. However, synthetic surfactant also led to a 23% reduction in IVH, 27% in PDA, and 32% in BPD. When natural surfactant is given as prophylaxis (i.e. at or soon after birth, before the development of RDS), the reduction in mortality is 45% and the reduction in pneumothorax is 69%, but as with rescue therapy, there is no effect on the incidence of IVH or BPD. The effect on the incidence of PDA is an increase of 27%. When synthetic surfactants are given prophylactically, there is a similar reduction in mortality of 44% and a reduction in pneumothorax of 36%. The incidence of IVH and BPD is unchanged, but as with the natural surfactant, there is a small increase in the incidence of PDA of 27%. The main side effect is pulmonary hemorrhage that has been reported to occur in 4-7% of infants given surfactant. Although the administration of surfactant has had a dramatic effect on neonatal practice, it is likely that further studies will lead to more appropriate use of surfactant. *Key words: surfactant, respiratory distress syndrome, mortality, morbidity, side effects.*

Function of Surfactant

Although there has been great interest in the role of surfactant in the lung, it is also found in all cavities, including the joints, pleural and pericardial spaces. It then functions as a highly efficient lubricant with qualities far exceeding commercial engine oils!

It has been known since the late 1950s[1] that lack of surfactant in respiratory distress syndrome reduces lung compliance by increasing surface tension forces at the air/water interface within the alveoli. However, when a surfactant preparation is tested in the laboratory using the Wilhelmy balance, the effects initially seem disappointing as the surface tension of pure water is only reduced from 70 to

* From St. Thomas' Hospital, London.

** Professor of Neonatology, St. Thomas' Hospital.

approximately 40 dynes/cm. Adding plasma has a similar effect, while a detergent such as Tween 80 will reduce the surface tension force down to 30 dynes[2]. If, however, the surface area is then reduced by moving a strip in contact with the surface towards one end, the surface tension measurement will drop effectively to zero after the addition of surfactant, but remain at 30 when Tween 80 has been added[2]. This is an illustration of the third important role of surfactant, that of providing alveolar stability. This dynamic effect of surfactant results from the concentration of the monolayer of molecules each with a hydrophylic end in the water and hydrophobic end in the air space above. Thus, on expiration there is a continuous film of lipid lining the alveoli, rather like a waxy coating, and the water molecules are no longer in contact with the air. This also has the effect of solidifying the surface. This can be demonstrated by adding a very light object to the surfactant/water film in the Wilhelmy trough. While the surface area is relatively large, the object can readily be blown from side to side. When, however, the surface area is reduced so that the surfactant molecules are packed together, the object remains stationary despite vigorous blowing, indicating that the surface is no longer liquid[3].

The fourth function of surfactant is that of lung clearance. On each inspiration, surfactant molecules are recruited to the surface as the alveolar area increases. On expiration, there is then an excess of surfactant molecules which pass from the alveoli to the small airways.

In this way, micro-particles such as bacteria are carried on the surface film from the alveoli to the 14th and 15th division of the airways, where cilial action takes over the function of surfactant as the main lung clearance mechanism[4].

Role of Surfactant Proteins

Although the main constituents of surfactant are phospholipids, the major one being dipalmityl phosphatidyl choline, five to 10 percent consists of surfactant proteins. There has been increasing interest in recent years in the function of these different proteins. Surfactant A appears to have an important role in regulating the rate of surfactant secretion and recycling, and also improves surfactant structure[5]. Surfactant B enhances the formation of the surfactant monolayer and improves spreading[6,7]. It also has a direct effect in reducing surface tension. Surfactant C protein also enhances film formation, while surfactant D appears to have a role in surfactant metabolism and may be important in immune defenses of the lung[8,9]. Surfactant B and C are produced in relatively small quantities before 20 weeks' gestation, but then, unlike surfactant A, rise rapidly[10]. Surfactant B deficiency appears to be responsible for the occurrence of respiratory distress syndrome (RDS) in relatively mature babies born to diabetic mothers, and is also responsible for the occurrence of respiratory distress syndrome in term babies born to susceptible families[11].

The Physiological Effects of Surfactant Administration to Babies with RDS

As could be anticipated from physiological studies on surfactant function in the laboratory, respiratory distress syndrome is associated with stiff, small and relatively airless lungs. It is well documented that the administration of natural surfactant produces a rapid improvement in oxygenation so that the $aaDO_2$ may fall from 300-400 mmHg to 30-40 within 15 to 20 minutes. The effects of synthetic surfactant, such as Exosurf, are less dramatic. With this it is often difficult to determine whether the surfactant is having a therapeutic effect in less than six hours. It was anticipated that these improvements in oxygenation would be associated with corresponding improvements in the compliance measurements, indicating that the lungs were no longer so stiff. However, the majority of studies failed to show any improvement in compliance measurements obtained by relating the volume of gas entering and leaving the lung to the ventilator pressure swing, at any rate, until 12 or even 24 hours after the improvement in oxygenation[12, 13].

Other investigators have shown that improvement can be noted early provided that true, static compliance measurements are obtained[14]. These are achieved by occluding the airway at the end of inspiration, which will eliminate all respiratory effort via the Hering Breuer inflationary reflex, and then venting the gas from the lung to ambient rather than to positive end expiratory pressure (PEEP). An elegant study by Kelly et al.[15] confirmed very clearly that improvement in lung compliance can only be demonstrated early after the adminstration of surfactant, if this method of measuring compliance is used, rather than purely by relating the tidal volume to the ventilator pressures.

There have now been a small number of studies measuring the lung volume of babies requiring ventilatory therapy for respiratory distress syndrome, both before and after administration of surfactant. These have usually depended on measuring the concentration of an insoluble tracer gas such as helium or argon in a small rubber bag within a cylinder, arranging for the ventilator to provide respiratory support to the baby via the bag rather than directly via the endotracheal tube for 30 to 45 seconds. These have shown that lung volume in severe respiratory distress syndrome may be as low as 5 ml/kg of body weight[16], compared to a normal of 25. Studies including our own[16, 17, 18] have shown that after natural surfactant, there is a rapid rise in lung volume, although not to normal levels[16, 18]. The effects of synthetic surfactants are less dramatic.

It is also possible to use this technique to measure the effective pulmonary blood flow, i.e., the blood supply to alveoli which are being adequately ventilated. This is achieved by adding a second test gas which is highly soluble in water, such as freon 22 or acetylene[19]. During the re-breathing period, the concentration of this gas will continue to decay, whereas the insoluble gas will stabilize after about

20 to 30 seconds. By knowing the solubility of the gas in plasma and the concentration of the soluble gas within the alveoli at each breath, it is possible to measure the effective pulmonary blood flow with good reproducibilty. These studies have shown that after natural surfactant, there is a significant increase in the effective pulmonary blood flow, although these improvements are smaller than the changes in the lung volumes[18].

It remains surprising to many people that surfactant therapy leads to improvement in lung volume and yet has no obvious effect on lung compliance as determined by the volume delivered by the ventilator. There have, however, been two studies which have helped to resolve this problem. The first one indicated that the major effects of surfactant therapy on the deflation curve of surfactant-deficient piglet lungs was at pressures of less than 5 cm H_2O, i.e., the pressure volume slope above this pressure was little changed by the addition of surfactant[19]. This indicated that surfactant was having its maximum effect at low inflation pressures, i.e., at or below the PEEP levels currently used. A further study examined the effects of PEEP on lung volumes before and after the administration of surfactant, also showing that the main effect of surfactant was at low lung volumes and pressure[20]. This raises the exciting possibility that as oxygenation improves after the administration of surfactant, small reductions in PEEP may so greatly increase the tidal exchange that the peak pressure can be reduced considerably.

Side Effects of Surfactant Therapy

There are now a number of studies showing that the rapid administration of large volumes of surfactant, for example, giving 5 mls/kg of body weight of Exosurf over two to three minutes, can produce increases in cerebral blood flow as measured by Doppler techniques[21]. These increases are in the order of 30 to 40 percent and are partially, although not totally, explained by a temporary increase in CO_2 retention due to poor ventilation. It would therefore seem sensible to give large volumes of fluid to the airway at a relatively slow rate. The second complication is that of pulmonary hemorrhage, which has been reported to occur in four to seven percent of babies given surfactant[2]. Hemorrhage is usually, though not always, relatively mild, but most authorities consider the presence of pulmonary hemorrhage to be contraindication to surfactant therapy. A third anxiety has been that giving natural surfactant, which inevitably contains animal protein, might induce immune responses in the months after its administration[23].

Finally, there has been some anxiety that the administration of surfactant might impair responses to infection within the lungs. It has been noted that the macrophages in particular tend to take up the surfactant, and concern has been

expressed that this might interfere with their function. There is however no clinical evidence that babies given surfactant have an increased incidence of lower respiratory tract infections, and indeed, increasing evidence that pre-term babies with congenital pneumonia are likely to be helped by surfactant administration.

Clinical Studies on the Role of Surfactant Therapy

There are now two synthetic and at least five natural surfactants available for the treatment of respiratory distress syndrome in pre-term babies. Although randomized controlled trials have been carried out, the majority of these have been relatively small. In order to make the best use of all the information available, a number of meta analyses have been carried out combining the information from a number of studies with similar designs. These have provided current knowledge as to the best way to give surfactant therapy. Studies on the role of natural surfactant given to infants who have established respiratory distress syndrome, i.e., rescue therapy, have shown that when compared to untreated infants there is a reduction in neonatal death of approximately 40 percent, with 95 percent confidence limits ranging from 16 to 57 percent. The incidence of pneumothorax is reduced by approximately 65 percent with confidence limits of 56-73 percent. There are, however, no apparent benefits regarding the incidence of intraventricular hemorrhage, patent ductus arteriosus or subsequent bronchopulmonary dysplasia. The results of synthetic surfactant given as rescue therapy (Exosurf) showed a similar effect with a reduction of approximately 40 percent in mortality and 48 percent (also below) in pneumothorax. Interestingly, Exosurf also led to a 23 percent reduction in IVH (confidence limits 3-38%) and a reduction in the incidence of patent ductus arteriosus of 27 percent (confidence limits 12-40%).

Of equal interest was the finding that Exosurf reduced the incidence of bronchopulmonary dysplasia by 32 percent (confidence intervals 1-54%). When natural surfactant is given as prophylaxis, i.e., at or soon after birth and before the development of respiratory distress syndrome, the reduction inmortality is slightly greater at 45 percent, with a confidence limit of 20 to 62 percent[24]. The pneumothorax rate showed a dramatic reduction by 69 percent, but as with rescue, there was no effect on the incidence of intraventricular hemorrhage or bronchopulmonary dysplasia. The effect on the incidence of patent ductus arteriosus was the opposite of that seen after rescue with synthetic surfactant, i.e., a small increase of 27 percent (confidence limits 3-57%). When synthetic surfactants including ALEC were given prophylactically, there was a similar reduction in mortality of 44 percent (confidence limits 26-57%) and a reduction in pneumothorax of 36 percent. The incidence of IVH and bronchopulmonary dysplasia was unchanged; however, as with the natural surfactant, there was a small increase in the incidence of patent ductus arteriosus of 27 percent, but no effect on the incidence of bronchopulmonary dysplasia[24].

The question of how many doses of surfactant should be given is obviously of considerable interest to clinicians. Current data indicates that with natural surfactant, two doses are preferable to one[25], but that with Exosurf, a synthetic surfactant, four doses have no advantage over two[26]. The number of infants included in studies comparing prophylaxis with rescue treatment has been relatively small. A meta analysis on these carried out by Soll suggested that prophylactic therapy[27] was probably associated with a reduction in the incidence of pneumothorax, but there was insufficient evidence to show a benefit in terms of mortality, IVH or bronchopulmonary dysplasia for either form of therapy.

Our information on the relative efficacy of synthetic and natural surfactants is also limited, but the latest meta analysis indicates that a natural surfactant (Survanta) will reduce mortality by approximately 10 percent more than will a synthetic surfactant (Exosurf). The author calculated that the use of a natural surfactant will save the life of an additional baby for every 33 treated.

Although the administration of surfactant has had a dramatic effect on neonatal practice, it is likely that further studies will lead to more appropriate use of surfactant. In the near future it is likely that synthetic surfactants will be available to which genetically engineered human surfactant proteins will have been added. Hopefully, these preparations will eventually become relatively inexpensive, and certainly would have the advantage that they would be totally free from foreign proteins.

Conclusion

We now have considerable information on the biochemistry and the physiological effects of surfactants. Although further fine tuning is likely to take place, we do now have sufficient information on how to use the currently available surfactant preparations effectively. There remains the problem of cost. It is hoped that in the next few years, market forces will improve so that infants throughout the world can have access to this life-saving form of therapy.

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EXOGENOUS SURFACTANT THERAPY IN NON-RESPIRATORY DISTRESS SYNDROME*

*Anne Greenough PhD***

SUMMARY: Greenough A. (Department of Child Health, King's College School of Medicine and Dentistry, London, United Kingdom). Exogenous surfactant therapy in non-respiratory distress syndrome. Turk J Pediatr 1996; 38: 45-50.

There is clinical evidence of the benefit of exogenous surfactant therapy to certain neonates with severe respiratory failure, diaphragmatic hernia, pneumonia and meconium aspiration syndrome. There still remain, however, important unanswered questions regarding, for example, optimum dosage and method of administration; appropriate randomized trials must be undertaken. *Key words: surfactant replacement therapy, neonatal respiratory disorders.*

Exogenous surfactant replacement therapy (SRT) has a well-established place in the treatment of respiratory distress syndrome. Data, however, are becoming available that SRT may also have a role in the management of other neonatal respiratory disorders[1]. The aim of this review is to examine the evidence for surfactant dysfunction/deficiency in such disorders and the efficacy of SRT in animal models and infants.

Severe Respiratory Failure

Bronchoalveolar lavage (BAL) studies[2] have demonstrated that in adult respiratory distress syndrome (ARDS) there is reduction in dipalmityl phosphatidylcholine and increasing accumulation of proteinaceous edema fluid which interferes with the alveolar surfactant monolayer. Studies involving animal models, however, have suggested that the response to SRT will depend on the mechanism by which ARDS has been produced; SRT is only effective in restoring the pressure-volume characteristics of an ARDS model created by serial lavage resulting in progressive surfactant depletion, but not in those involving hypoxia resulting in proteinaceous edema or administration of an antibody to surfactant protein B (SP-B).

In clinical use, surfactant replacement therapy has been particularly useful in infants who are described as having respiratory distress syndrome (RDS) at term. Infants, all greater than 37 weeks of gestational age with an a/A ratio ≤ 0.23, were given Survanta (100 mg/kg in up to four doses)[3]. Twenty-three of the 29 patients had a clinically significant response, that is greater than a 25 percent reduction in the oxygen index. Prior to surfactant the mean oxygen index was

* From the Department of Child Health, King's College School of Medicine and Dentistry, London.

** Professor of Clinical Respiratory Physiology, King's College School of Medicine and Dentistry.

30, and SRT significantly reduced this to 12 ($p < 0.01$)[3]. In contrast, in seven infants with severe respiratory failure due to either pneumonia, aspiration of blood or hemorrhagic pulmonary edema, all of whom required a mean peak pressure of 30 cmH_2O and at least 90 percent inspired oxygen concentration, the response to Curosurf was variable. A rapid improvement in two patients, show improvement in four and no improvement in one patient occurred, although there were no side effects.

Surfactant "deficiency" has also been demonstrated in infants whose respiratory failure was so severe they needed axtracorporeal membrane oxygenation (ECMO). In a group of such patients[4], 18 with meconium aspiration syndrome and four with pneumonia, serial sampling of tracheal aspirates for phospholipid and surfactant protein A (SP-A) content demonstrated a mean increase of 200 percent in the levels in the 72 hours prior to weaning from ECMO. Those infants with the greatest improvement in surfactant status had the fastest weaning from ECMO. The results suggested that SRT could have a role in shortening the duration of ECMO. That hypothesis was tested by administering Survanta (up to four doses) to infants requiring ECMO for meconium aspiration syndrome, group B streptococcal sepsis with pneumonia, respiratory distress syndrome and pulmonary hypertension of the newborn[5]. On days 2 and 3, the compliance of the infants who had received surfactant was significantly greater than that of the placebo group. There was also a trend in the surfactant group towards a shorter time to extubation and duration of oxygen therapy, as well as a younger age at discharge. The only statistically significant difference, however, was the duration of ECMO, being a mean of 107 hours in the surfactant group and 139 hours in the control group (5).

Congenital Diaphragmatic Hernia (CDH)

Biochemical immaturity of the surfactant system has been demonstrated in several animal models. Comparison of neonatal rats with or without diaphragmatic hernia (CDH) demonstrated, not surprisingly, that the rats with CDH had lower lung weights, DNA and protein contents as well as lower amounts of disaturated phosphatidylcholine. Similarly, in a lamb model in which a diaphragmatic hernia was created surgically at 80 days of gestation, the lambs with CDH compared to the controls not only had smaller lungs, lower total lung capacity and reduced compliance, but also a reduction in the percentage of phosphatidylcholine and an increase in lavage protein and surface tension. SRT in such a lamb model resulted, therefore, in predictable improvements. Fifty mg/kg of Infrasurf in "CDH" lambs was associated with a significant improvement in oxygenation, compliance and lung volume when compared to controls.

In humans, there is also evidence for surfactant abnormalities in CDH-affected patients[6]. The lung compliance and pressure-volume loops of such patients are

similar to surfactant-deficient infants. Hyaline lung membrane formation, immature amniotic fluid lecithin: sphingomyelin (L:S) ratios and absence of phosphatidyl glycerol in the amniotic fluid are found postmortem. There is a differential effect between the lungs, with the ipsilateral lung being more affected than the contralateral lung, as evidenced by a decrease in the phospholipid fraction. To date in the literature, however, there is very little evidence to suggest that SRT is efficacious in infants with CDH. Three infants who received 100 mg/kg of Infrasurf prior to the first breath have been reported. The patients survived despite a predicted mortality of 80 percent[7]. This mortality was estimated as the infants all had prenatal diagnosis, polyhydramnios, dilated stomach in the chest, a patch closure of the defect and a ventilation index greater than 1000.

Pneumonia

In all types of animal models, in "infective" pneumonia there is evidence of surfactant dysfunction and some evidence of SRT efficacy. For example, influenza virus adversely affects the type II pneumocytes, reducing the phospholipid content. In such a model, SRT improved survival from zero to 75 percent Mycoplasma pneumonia is associated with reduction in lung compliance, abnormal lung pressure-volume curves, a decrease in sphingomyelin and an increase of palmitic acid. In humans, BAL studies have shown that in bacterial pneumonia there is reduced surface tension, SP-A and lung lavage phospholipids. In an animal model of bacterial pneumonia, SRT improved lung compliance to normal levels. There is some evidence to suggest that gram-negative rather than gram-positive bacterial pneumonia may be more deleterious to the surfactant system and that this may be an endotoxin effect. The endotoxin may cause injury to the type II cells, producing an abnormal quantity and composition of surfactant, with a reduced L:S ratio, phosphatidyl glycerol and amount of palmitic acid in the phosphatidyl choline. Functional changes also occur as evidenced by a reduction in total lung capacity, static compliance and diffusing capacity, with an increase in pulmonary arterial pressure. There is also evidence to suggest that aspiration pneumonia, involving acid aspiration and pulmonary edema, is associated with a reduction in surfactant function and hyaline membrane formation. In a rabbit model of aspiration, SRT improved lung recoil.

One study has suggested that surfactant treatment of congenital pneumonia may improve respiratory status[8]. Fourteen infants, with either meconium aspiration syndrome or pneumonia and requiring an inspired oxygen concentration of 1.0 and a mean airway pressure of 13-15 cmH_2O with a pre-treatment a/A ratio of 0.09, were given 90 mg/kg of calf lung surfactant extract (CLSE). A further three doses were administered if they still required an inspired oxygen concentration greater than 0.5 and a mean airway pressure of at least 7 cmH_2O. The first dose

of SRT was associated with an immediate improvement in the a/A oxygen ratio. None of the infants required ECMO, died or was oxygen-dependent for more than 14 days.

Our own experience using a synthetic surfactant (Exosurf) has been more mixed; certain infants have showed a rapid improvement in oxygenation as shown by a decline in $AaDO_2$, others have shown no improvement and some have subsequently had a pulmonary hemorrhage. There has been reported a similar mixed response to Alveofact; 15 infants who reguired an inspired oxygen greater than 0.5 and peak inspiratory pressure greater than 22 cmH_2O were given 50 mg/kg of Alveofact eight hours after birth. They received three further doses of Alveofact if necessary, but unfortunately they required the same inspired oxygen concentration 12 hours after treatment as pre-treatment. Ten of the infants died, four of respiratory failure, four of sepsis and two of intracranial hemorrhage[9].

Meconium Aspiration Syndrome (MAS)

Meconium has been shown to displace surfactant from the alveolar surfaces and inhibit surfactant's surface tension lowering function. This, however, can be overcome if a high enough concentration of surfactant is given[10]. The effect of human meconium is dose-dependent. In an experimental newborn rabbit, 65 mg/ml of human meconium resulted in a 27 percent reduction in lung thorax compliance, whereas 130 mg/ml brought about a 38 percent reduction. Separation of human meconium into the water methanol soluble phase (protein and bilirubin) and the chloroform soluble phase (fatty acids, triglyceral and cholesterol) demonstrated the latter to have the highest activity against surfactant, as measured in a pulsating bubble[11].

Studies in animal models of MAS have demonstrated some efficacy of SRT. Animals given 3 mg/kg of human meconium showed a 30 percent improvement in oxygenation following administration of CLSE immediately and 67 percent at one hour. This was also associated with no change in compliance, and a 44 percent increase in resistance[12]. In a piglet model, lavage with Survanta was more efficacious than saline lavage or suction only. Although there were no radiographic or pathological differences between the groups, immediate improvement in oxygenation, as shown by a decrease in the oxygen index, was demonstrated in the surfactant lavage group[13].

Experience in human infants has been variable. In infants greater than 37 weeks gestation with a/A ratios less than 0.23, Survanta (100 mg/kg up to six doses) resulted in 14 of 20 infants having a clinically significant response, that is a greater than 25 percent reduction in the oxygen index. Only one infant deteriorated. The mean oxygen index pre-surfactant was 36 and at one hour post-surfactant

was 24[3]. Our own experience with Exosurf has been mixed; some infants had a modest improvement in oxygenation, but certain infants went on to require high frequency oscillation (HFO), one infant died and another ultimately had to be rescued by ECMO. Similarly, with Alveofact (50 mg/kg, one to four doses) begun at four to eight hours, there was a varied response: six of 10 infants did not respond, and although no infant deteriorated and all survived, two infants required HFO and one ECMO.

Conclusion

Preliminary evidence from clinical studies suggests that SRT may be useful in a variety of neonatal respiratory disorders. Key issues still, however, need to be addressed before this therapy can be used optimally in non-RDS respiratory failure. For example, the characteristics of those patients most likely to benefit should be identified. Pilot data suggests natural rather than artifical surfactant to be most useful, but there are no comparative studies. Dosage should be carefully determined, although in meconium aspiration syndrome, existing results suggest that a dose regimen higher than that used in RDS should be employed. The method of administration may also influence efficacy; lavage or nebulization could offer advantages.

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CARCINOMA OF THE COLON IN CHILDREN*

*Münevver Büyükpamukçu MD***, *Semha Berberoğlu MD****
*Nebil Büyükpamukçu MD*****, *Faik Sarıalioğlu MD******, *Gülsev Kale MD*******
*Canan Akyüz MD********, *Tezer Kutluk MD*********

SUMMARY: Büyükpamukçu M, Berberoğlu S, Büyükpamukçu N, Sarıalioğlu F, Kale G, Akyüz C, Kutluk T. (Oncology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Carcinoma of the colon in children. Turk J Pediatr 1996; 38: 51-58.

The symptoms, histology, extent and course of disease in 16 adolescents with colorectal carcinoma who were admitted to Hacettepe University Children's Hospital between 1972 and 1990 are presented. Most patients presented with vague abdominal complaints. Twelve of the 16 patients had mucin-producing adenocarcinoma. Extensive disease at diagnosis and unresponsiveness to medical management were determined. Only one patient survived free of disease four years after diagnosis. Nine of the patients died between one day and one year following the initial surgery. The remaining six patients were very ill when they were discharged from the hospital, after which time no information was received concerning them. *Key words: colorectal carcinoma, childhood tumors.*

Carcinoma of the large bowel is rare in individuals under 20 years of age[1]. Colonic cancer is more common in the Western world than in rural Africa[1]. This difference is thought to be related to the longer transit time of fecal material in the bowels of persons consuming relatively low-fiber diets[1,2].

Although there are approximately 145.000 new cases of colorectal carcinoma in adults annually[1], the Surveillance, Epidemiology, and End Results (SEER) data suggest that only about 80 cases of colorectal carcinoma occur annually in the United States in individuals under 20 years of age, since the incidence of this tumor is approximately one per million in this group[1]. In children and adolescents, these tumors may occur at any site in the large bowel and are not usually associated with a family history of large-bowel cancer[1].

During the period from 1972 to 1990 at Hacettepe University Hospital, there were 4.749 nonleukemic, malignant tumors encountered in patients from birth to age 17. Nineteen of them originated from the gastrointestinal tract (0.4%). There were

* From the Oncology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara.
** Professor of Pediatrics and Pediatric Oncologist, Hacettepe University Faculty of Medicine.
*** Pediatric Oncologist, Ankara Oncology Hospital, Ankara.
**** Professor of Pediatric Surgery, Başkent University Faculty of Medicine, Ankara.
***** Professor of Pediatrics and Pediatric Oncologist, Dokuz Eylül University Faculty of Medicine. İzmir.
****** Professor of Pediatric Pathology, Hacettepe University Faculty of Medicine.
******* Associate Professor of Pediatrics and Pediatric Oncologist, Hacettepe University Faculty of Medicine.

two malignant neoplasms of the stomach and one malignant tumor of the pancreas. The remainder were 16 carcinoma of the colon and rectum, and these are presented in this report. Thus, colonic neoplasms represented 0.33 percent of all cancers seen in roughly the first two decades of life at Hacettepe University Hospital during the study period.

Material and Methods

For the 16 subjects, the age at diagnosis ranged from 11 to 16 years, with a median age of 13 years (Table I). There were nine boys and seven girls in the patient group. Each year from 1972 to 1990, one or two patients were diagnosed. There was no increase in the number of patients according to years.

Table I: Characteristics of Patients with Colorectal Carcinoma

Pt.	Age	Sex	Primary Site	Histology*	Stage at Diagnosis	Documented Metastases at Diagnosis	Operation	Survival
1.	13 yr	M	Rectum	Mucoid	D	Mesenteric nodes, peritoneum	Abdomino-Perineal resection	Died in 6 months
2.	14 yr	F	Rectum	Non mucoid	D	Liver	Refused operation	Died in 1 month
3.	13 yr	F	Recto sigmoid	Non mucoid	C	Iliac nodes (+)	Abdomino-perineal resection	Died in 6 months
4.	11 yr	M	Transverse colon	Non mucoid	D	Intra-abdominal diffuse metastases to liver, abdominal wall, peritoneum	Exploratory laparotomy; biopsy	Died first postoperative day
5.	14 yr	F	Rectum	Mucoid	D	Peritoneum	Exploratory laborotomy; transverse loop colostomy	No follow-up
6.	13 yr	M	Rectum	Non mucoid	D	Peritoneum	Abdomino-perineal resection	Died in 9 months
7.	12 yr	M	Sigmoid	Mucoid	D	Omentum, peritoneum	Exploratory laparotomy; biopsy	No follow-up
8.	13 yr	M	Cecum	Mucoid	C	Mesenteric nodes	Ileocecal resection; ileocolic anastomoses	Followed 4 yrs, no follow-up further
9.	16 yr	M	Hepatic flexure	Mucoid	C	Mesenteric nodes	Ileocecal resection; ileocolic anastomoses	Died in 1 year
10.	15 yr	F	Decending colon	Mucoid	D	Mesenteric nodes, peritoneum, omentum	Transverse loop colostomy	Died in 6 months

Pt.	Age	Sex	Primary Site	Histology*	Stage at Diagnosis	Documented Metastases at Diagnosis	Operation	Survival
11.	11 yr	F	Recto sigmoid	Mucoid	D	Mesenteric nodes, peritoneum	Rectosigmoid resection; colostomy	Died in 8 months
12.	16 yr	M	Sigmoid	Mucoid	D	Omentum, peritoneal carcinomatosis	Exploratory laparotomy; biopsy	No follow-up
13.	14 yr	F	Rectum	Mucoid	D	Peritoneall carcinomatosis	Colostomy	No follow-up
14.	13 yr	M	Sigmoid	Mucoid	C	Mesenteric nodes	Sigmoid colon resection, colostomy	No follow-up
15.	14 yr	M	Hepatic flexure	Mucoid	D	Omentum, mesenteric nodes	Ileocecal resection	Died in 12 days
16.	13 yr	F	Transverse colon	Mucoid	D	Omentum, mesenteric nodes	Exploratory laparotomy, biopsy	Died in 1 month

* All histopathologic diagnoses were adenocarcinomas.

There was no history of ulcerative colitis, familial polyposis or any other precancerous lesion in any of the patients.

The primary tumors were located throughout the large bowel. One primary tumor arose in the cecum, two in the hepatic flexure, two in the transverse colon, one in the descending colon, three in the sigmoid, two in the rectosigmoid, and five in the rectum (Fig. 1).

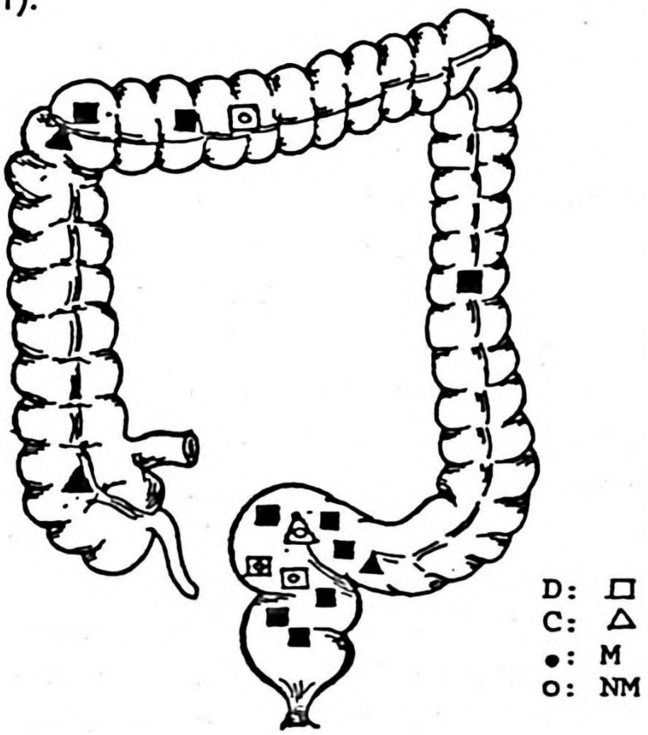

Fig. 1: Distribution, histologic features and stages of colon cancer.
D : Dukes' stage D. C : Dukes' stage C.
M : mucinous type of adenocarcinoma. NM : nonmucinous histologic findings.

The most common presenting symptom was abdominal pain, which was observed in 11 of the 16 patients. This was followed by rectal bleeding, abdominal distention, weight loss, nausea, vomiting, anorexia and intestinal obstruction. Palpable abdominal mass, diarrhea and constipation were also seen. No particular site was found to be associated with any specific symptom, although all patients with rectal or sigmoid primary tumors presented with rectal bleeding, and one complained of rectal pain.

The duration of symptoms prior to diagnosis ranged from two weeks to two years (median three months).

Four patients (patients 2, 3, 4 and 6) had nonmucinous adenocarcinoma. The remaining patients had mucin-producing carcinomas.

Most of the subjects were seen with extensive disease at diagnosis[3] (Table I). In six patients abdominal ultrasonography and in seven patients barium enema colon graphy was performed. Although there are several staging systems for colorectal carcinoma, using the modified Dukes' staging system (Table II) four patients had stage C disease, and 12 had stage D disease.

Table II: Modified Dukes' Classification Colorectal Carcinoma[3]

Stage	Description
A	Lesion confined to bowel wall
B	Direct extension to serosal fat without lymph mode involvement
C	Lymph node involvement
D	Distant metastases (may include extranodal intraabdominal tumor, lung, brain, bones, etc.)

The clinical follow-up of all patients illustrated the nature of the disease (Table I). In addition to the extensive intra-abdominal tumor, involvement of distant organs such as the lungs was detected in one patient. Adjacent invasion, tumor seeding and metastases to the intraabdominal organs were found during surgery in all of the stage D patients.

Surgical procedures were categorized according to the extent of initial surgical resection. In four patients laparotomy revealed an unresectable lesion or widespread intra-abdominal disease, and only incisional biopsies were performed. In another group of three patients, palliative colostomies were performed. Segmental resection was defined as resection of the involved segment along with margins of less than five centimeters. Two patients had resection and colostomy of the rectosigmoid area. Another group of three patients had resection and anastomoses of the right colon. Complete resection of the rectum was performed in three patients by abdominoperineal resection. The procedure included resection of a wide segment of the colon and its mesentery. One patient refused surgery and only rectal biopsy was performed.

Most patients had significant residual tumor after the initial surgical procedure. The chemotherapy used to treat six of these patients consisted of 5-fluorouracil. Another six subjects received 5-fluorouracil and cyclohexylnitrosourea (CCNU), and a group of three subjects received 5-fluorouracil. adriamycine and mitomycine. None of the patients could be followed up to determine the long-term survival and the effects of chemotherapy. The only long-term survivor of this entire group (patient 8) had a primary cecum tumor, was treated with ileocecal resection and ileocolic anastomoses, and received 5-fluorouracil and CCNU for 14 months. He was followed in continuous remission for four years. No information concerning him was received after this period.

Discussion

It is not known whether there is an increasing rate of colon cancer in young individuals or whether the median age of all individuals with colon cancer is decreasing.

The differences in duration of symptoms, primary site, pathologic findings, stage and prognosis between adults and children are striking[4, 5]. A continuing problem affecting prognosis in children is the delay in diagnosis. The initial and most common symptoms of vague abdominal pain coupled with constipation and diarrhea are not indicative of malignancy. Anemias are treated routinely without arousing the physician's suspicions. Adolescents generally do not wish to relate rectal bleeding with cancer, and are unlikely to volunteer this information. Screening methods as used for adults are not feasible in children except in those instances of predisposing conditions[3, 6-8]. An awareness that colorectal cancer can occur, and more detailed attention to symptoms, could conceivably increase the rate of earlier diagnosis. In our patients the most common symptoms were abdominal pain and rectal bleeding.

The predominant histologic pattern noted in 12 of the 16 patients was that of mucin-producing adenocarcinoma. This subtype occurs in five to 15 percent of adult patients[5, 9] but has been reported for most of the tumors of children and adolescents[1, 4, 7, 10, 11]. Tumors may grow to huge sizes because of the pooling of mucin.

Although no sex predominance has been reported among adults[12-14], there is a notable preponderance of males among young patients[13, 15, 16]. Nine of 16 patients in this series were boys.

Regarding the primary tumor site, 60 percent of adult patients are found to have their primary located within 25 cm of the anus. The rectum and sigmoid are also common primary sites for mucinous adenocarcinoma in adults, occurring in 33 and 27 percent of cases, respectively[9]. This preponderance has not been found in young subjects. In 79 children reviewed by Anderson and Bergdahl[15],

the most common site was the transverse colon (39%), compared with two of 16 in this series (12.5%). In our patients the most common primary site was the rectum (31%).

The survival of our patients was influenced by the very advanced stage of disease at presentation, which was the most important clinical aspect of these adolescents with colorectal carcinoma[13]. Prolonged duration of symptoms and delay in diagnosis may have contributed significantly to the poor outcome for these patients. In this series, 12 of the 16 patients had widespread intraabdominal disease at the time of diagnosis; all had extension of the primary tumor beyond the bowel wall. The only long-term survivor in this group (patient 8) had no residual tumor following definitive surgery. We could not follow our patients for a long period. One of them died on the first post-operative day, while eight died between 12 days and one year after the initial surgery. The remaining seven patients were very ill when they were discharged from the hospital. No information concerning them was received after that time. The median survival time was six months in the patients who were able to be followed.

The survival pattern for our patients corroborates the results of the series reported by Andersen and Bergdahl[15] in which only two of 38 patients who underwent "curative" surgery survived more than five years, and the results of the series reported by O'Brien[17] in which only three of almost 200 patients survived five years or more. Delayed diagnosis, locally invasive, aggressive metastatic behavior and poor responsiveness to nonsurgical modalities of treatment were major determinants in the poor prognosis for these young patients. These data are in marked contrast to the data that have been reported for adult patients with colorectal carcinoma[18]. For 120 adults with mucinous carcinoma, as reported by Symonds and Vickery[9], the five-year survival was 53 percent.

Current therapy is unsatisfactory for several reasons. Colorectal carcinomas are detected after development of disease extension in adolescents[1, 16, 19]. Colon carcinoma is one of the most unlikely diagnoses for a teenager and is therefore unsuspected by the pediatrician, in ternist or surgeon examining a patient with diffuse abdominal discomfort or a mass. Another reason for concern is that surgery is the only modality known to be effective in providing cures. Adjuvant chemotherapy extends the life of individuals during childhood. Few patients who present with extensive metastatic disease are cured with chemotherapy[20]. Radiation has little to offer this tumor except when the tumor involves the rectosigmoid or anal areas.

Future considerations include determination of the implications of the DNA labeling index for the response to chemotherapy, refinement of the tumor cloning assay for prediction of the response to treatment, determination of the impact of specific histologies for the response to various chemotherapeutic agents, and greater integration of new therapeutic modalities in the management of these uncommon childhood tumors[1].

In conclusion, cancer of the colon should not be excluded from a clinical diagnosis in childhood on the basis of age alone. However, symptoms in children with abdominal pain are generally associated with mesenteric lymphadenitis, gastroenteritis and appendicitis, whereas in adult patients cancer of the colon would be considered.

It is suggested that barium enema x-rays be performed more frequently in children who have abdominal pain or vague abdominal symptoms persisting more than three weeks. Rectal bleeding is another symptom which has to be taken into consideration in the diagnosis of colorectal malignancies in childhood.

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DIALYSIS TREATMENT IN CHILDREN WITH AMYLOIDOSIS DUE TO JUVENILE RHEUMATOID ARTHRITIS*

*Maria Sieniawska MD***, *Maria Roszkowska - Blaim MD****

*Beata Wojciechowska MD*****

SUMMARY: Sieniawska M, Roszkowska-Blaim M, Wojciechowska B (Nephrology Unit, Department of Pediatrics, University Children's Hospital, Warsaw, Poland). Dialysis treatment in children with amyloidosis due to juvenile rheumatoid arthritis. Turk J Pediatr 1996; 38: 59-66.

Rapid deterioration of renal function in amyloidotic children may be due to progression of amyloidosis or exacerbation of chronic renal failure (CRF). Continuous ambulatory peritoneal dialysis (CAPD) is superior to hemodialysis (HD) both in end-stage renal disease and in exacerbations of CRF in amyloidosis.

A better supply of protein and easier control of hypertension are possible on CAPD, while HD is associated with the risk of hypovolemia episodes, cardiovascular disturbances and bleeding connected with heparinization. *Key words: renal amyloidosis, continuous ambulatory peritoneal dialysis, chronic renal failure.*

Systemic amyloidosis is an important cause of morbidity and mortality in juvenile rheumatoid arthritis (JRA). Renal involvement manifests itself as nephrotic syndrome (NS) with a variable degree of renal damage and may progress to end-stage renal disease (ESRD)[1-6]. The current thinking about renal replacement therapy in children with amyloidosis is mixed. The purpose of this study was to assess the progress of disease and the results of dialysis treatment in children with JRA and amyloidosis.

Material and Methods

Eight children with JRA and amyloidosis were referred from the Institute of Rheumatology between 1980 and 1991 because of deterioration of renal function. Their disease met the American Rheumatic Association's criteria for diagnosis of systemic JRA[7]. The patients' ages at onset of JRA ranged from 1.3 to 8.3 years.

Amyloidosis was suspected when proteinuria or frequent exacerbations of JRA appeared. NS was defined as proteinuria greater than 50 mg/kg/day and a serum albumin level less than 2.5 g/dl. Renal insufficiency was diagnosed when the serum creatinine level exceeded the upper normal laboratory limit of 1.0 mg/dl.

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* From the Nephrology Unit, Department of Pediatrics, University Children's Hospital, Warsaw.

** Professor of Pediatrics, University Children's Hospital.

*** Assistant Professor of Pediatrics, University Children's Hospital.

**** Pediatrician, University Children's Hospital.

Amyloidosis was confirmed by renal and/or gingival biopsy in all patients. The biopsy specimens were stained for amyloid with Congo red[8] and Sirius red[9].

Prior treatment of JRA consisted of non-steroidal anti-inflammatory drugs (NSAID) in all patients. The next medication for disease control was corticosteroids at a daily dose of 0.5-1.0 mg/kg depending on JRA activity. During exacerbations of JRA, children received methylprednisolone intravenously.

Chlorambucil at an initial daily dose of 0.1 mg/kg was given to patients (Cases 1, 3, 4, 5, 7, 8, Table I) when proteinuria appeared. For active, severe polyarthritis and the presence of active extraarticular features (fever, hepatosplenomegaly), Cases 1 and 3 received cyclophosphamide, and Case 3 colchicin, but without good effects.

Table I: Characteristics of Patients with Amyloidosis

	Age Diagnosis (years)						
Patient	JRA	Proteinuria	NS	Renal Failure	Creatinine at Renal Insufficiency Diagnosis (mg/dl)	Age at Biopsy: Renal* Gingival**	Age at Start of Dialysis: (years)
1	4 6/12	–	8 3/12	10 7/12	1.3	8 5/12*	11
2	3 9/12	–	7 5/12	7 5/12	4.6	7 6/12*	7 5/12
3	8 4/12	9 10/12	11 5/12	11 5/12	1.2	10 5/12*	11 7/12
4	8	9 10/12	11 10/12	12 5/12	2.5	9 10/12**	14 11/12
5	3 3/12	–	5 10/12	9 4/12	9.2	6*	9 10/12
6	3 10/12	5 7/12	6 4/12	8 5/12	1.8	8 7/12*	8 6/12
7	1 4/12	10 7/12	12 9/12	12 9/12	1.51	11 1/12*	15 2/12
8	2	–	7	7 7/12	1.1	4**	–
						9 3/12*	

The course of the disease in all patients is shown in Table I. All patients with chronic renal failure (CRF) during the predialysis period and on hemodialysis (HD) were given a diet recommended for height age. A high-protein diet (protein > 2g/kg/day) was given to patients on continuous ambulatory peritoneal dialysis (CAPD).

All children underwent dialysis (HD and/or CAPD). The indications to start dialysis treatment in cases 1, 2, 3, 4 and 8, despite relatively low creatinine levels, were rapid increase of BUN and creatinine level, acidosis, decreased diuresis, in Cases 2, 3, 4, 7 and 8, and ESRD in Cases 5 and 6 severe overhydration and hypertension (Table II).

HD was performed three times weekly for an average of nine hours per week. CAPD was started with four to five exchanges per day. If renal function improved, the initial regimen was reduced to three exchanges.

Table II: Data of Dialyzed Patients

Patients	Creatinine Before Exacerbation mg %	Creatinine mg/dl	BUN mg/dl	Albumin g/dl	Proteinuria mg/kg/d	Diuresis ml/kg/d	Acidosis	BP mmHg	Months on Dialysis HD	Months on Dialysis CAPD	Outcome
1	0.57	5.8	94	2.5	70	37.5	+	↑	3	12	ESRD after exacerbations of JRA BP, transplanted
2	0.96	6.0	120	2.0	110	12.5	+	–	0.5	3	Improvement of Renal Function, BP°
3	0.8	6.3	95	1.8	188	19.0	+	↑	1	3	
4	1.9	5.0	117	1.5	480	11.5	+	↑	0.5	–	Cardiovascular disturbances, BP°, died
5	6.0	13.0	64	2.6	250	20.0	–	↑	–	17	ESRD, BP°°, Good rehabilitation
6	1.8	16.0	84	1.6	250	9.0	–	↑	12	–	ESRD, BP°°, Cardiovascular disturbances, died
7	1.51	6.63	114	4.8	70	20 → 0	–	↑	5/12	10	ESRD, BP°°, Good rehabilitation
8	1.67	2.55	76	3.4	128	50	+	↑	–	3	ESRD, BP°°, Good rehabilitation

BP° : normal blood pressure.

BP°° : good control of blood pressure.

The serum creatinine level and BUN were checked after a three-day interval without dialysis. Renal ultrasound (US) was performed with a Siemens SL Unit with 3.5 and 5 MHz transducers operating in real time. The size of the kidney was evaluated in relation to the child's height[10].

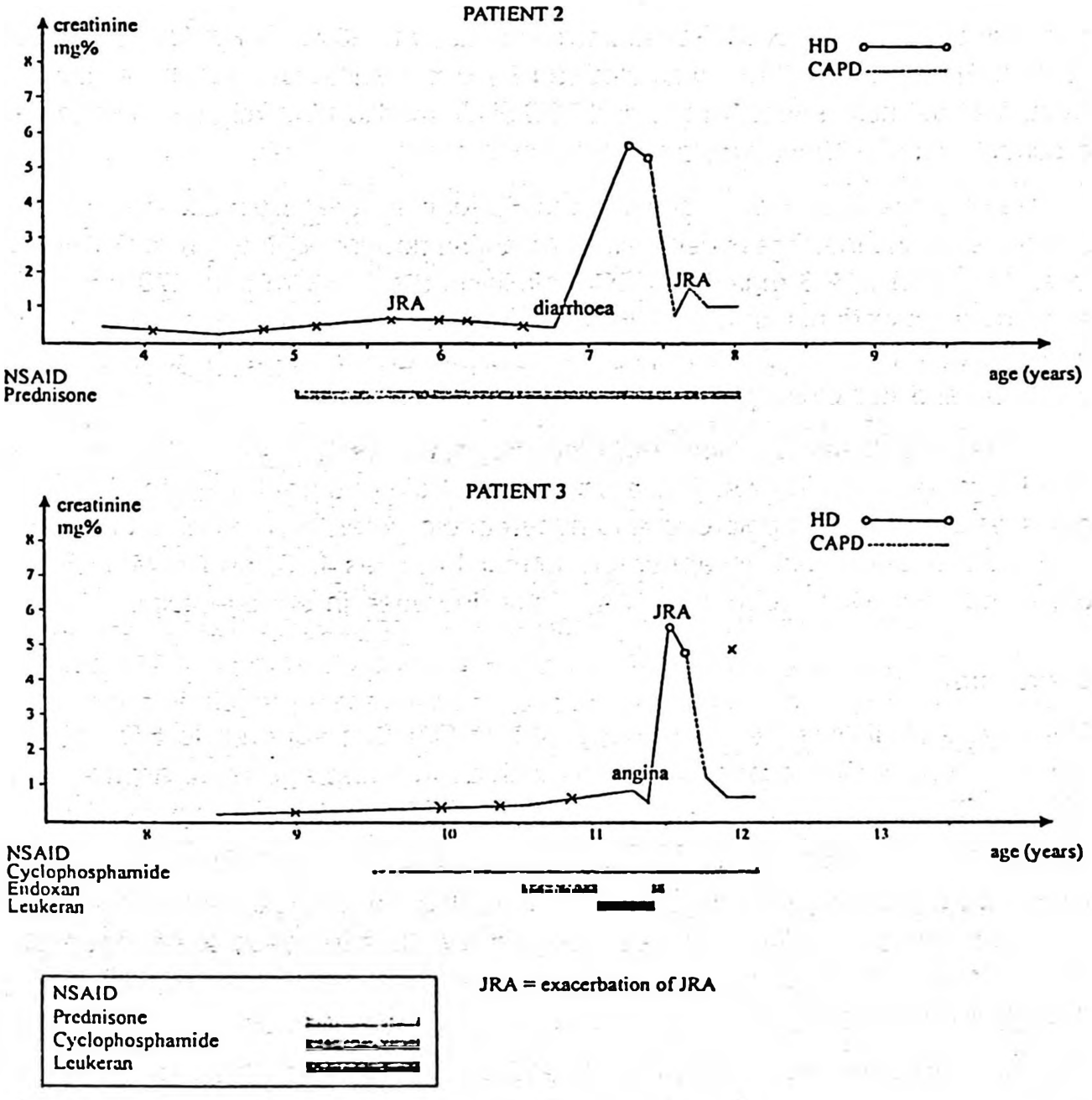
Results

The data of the dialyzed patients are shown in Table II. Progressive weakness, weight loss, diminishing diuresis, and bleeding from the gastrointestinal and respiratory tracts were observed in Case 1 over three months on HD. Considerable improvement of his general condition, regression of articular features and good quality of life were achieved despite ESRD when the child was transferred to CAPD. After a year on CAPD the child was successfully transplanted.

Cases 2 and 3, after 15 days and one month, respectively, on HD with episodes of hypotension and no improvement in renal function, were transferred to CAPD. Over a period of three to four months their renal functions gradually improved (Table III, Figs 1-2).

Table III: Laboratory Data of Amyloidotic Children with Exacerbation of CRF Treated with CAPD

Patient	Time on Dialysis (months)		Creatinine mg/dl	Diuresis ml/day	Proteinuria mg/kg/day	Effects
	HD	0.5	6.0→5.0	200	110	Oliguria
		1	5.0→1.8	1000	43	Renal function improvement
	C					
2	A					
	P	2	1.8→1.5	1400	46	
	D					
		3	1.5→1.3	1100	49	
	2 months after stopping dialysis		1.5	2000	75	
	HD	1	6.3→5.07	950	188	Oliguria Overhydration
		1	5.07→1.6	1000	36	Renal function improvement
	C					
	A					
3	P	2	1.6→1.3	1300	58	
	D					
		3	1.3→1.1	2000	63	
	2 months after stopping dialysis		1.1	1700	35	



Figs. 1-2: The course of disease and treatment regimen in two amyloidotic children.

After two weeks on HD, Case 4 died with signs of cardiovascular failure and myocardial ischemia.

After seventeen months on CAPD, Case 5 was in good condition, while case 6 on HD had frequent episodes of hypotension, hypertension and poor rehabilitation, and died after a year with signs of cardiovascular disturbance and gastrointestinal bleeding.

In Case 7, CAPD was started when the patient's serum creatinine level was 6.63 mg/dl and evaluated creatinine clearance (ECC) was 10.45 ml/min/1.73 m^2 with diminishing diuresis and coexisting hypertension requiring four antihypertensive drugs,

and after three months on CAPD, diuresis increased to 30-40 ml/kg/day, ECC was 12.37 ml/min/1.73 m^2. CAPD was stopped for one month, after which her serum creatinine level increased to 6 mg/dl and ECC diminished to 11 ml/min/1.73 m^2 despite a correct diet. CAPD was restarted.

After ten months Case 7 was transferred to HD for five weeks because of recurrent peritonitis. During that time hypertension and anuria developed, the serum creatinine level increased to 9.3 mg/dl and ECC diminished to 7.48 ml/min/1.73 m^2. JRA exacerbations were not observed. Prednisone was given at a daily dose of 5 mg, and she was transferred to CAPD again. Despite ESRD she is in good general condition and her blood pressure is well controlled.

US of the patients revealed various kidney sizes. Cases 1, 7 and 8 had normal-sized, hyperechoic kidneys. At the beginning of dialysis treatment, the kidneys of Cases 2 and 3 were enlarged and hyperechoic. After three months on CAPD their sizes and echogenicity appeared normal. In Cases 4, 5, and 6 with ESRD, the kidney size was reduced with a diffuse increase in echogenicity.

Discussion

The effects of dialysis treatment suggest that CAPD is superior to HD both in the treatment of CRF exacerbations as well as in end-stage renal amyloidosis (ESRA). Differentiation between exacerbation of CRF and ESRA may be difficult in children with rapid deterioration of renal function.

Repeated US is useful as it reveals transient kidney enlargement during CRF exacerbations and reduced kidney size with a diffuse increase of echogenicity in patients with ESRD, although the kidney size in renal amyloidosis is traditionally thought to be enlarged[11].

The early commencement of CAPD treatment in CRF exacerbations seems to be beneficial. HD treatment is definitely not tolerated as well by young amyloidotic patients than by children of the same age with other types of nephropathy.

CAPD makes it possible to avoid episodes of hypotension and bleeding during HD and improves control of hypertension which is particularly important when albumin infusions are necessary in overhydrated children with depleted intravascular volumes. Hypovolemia plays an important role not only in the development of CRF exacerbations but also in late prognosis. The nephrotic range of proteinuria despite advanced CRF was a characteristic feature in our patients, perhaps due to decreased renal tubular transport of protein in renal amyloidosis. CAPD made it possible to introduce a high-protein diet leading to improved protein balance. In some authors' opinions, in hypoalbuminemic adult patients with ESRA and heavy proteinuria, CAPD can worsen the condition[5].

In our patients on CAPD, increases in serum albumin levels were observed, despite heavy proteinuria. In three children treated initially with HD, a significant improvement was seen when they were transferred to CADP. In two of them in whom retrospective analysis of the course of the disease indicated exacerbation of CRF, a significant improvement of renal function was noticed after three months on CAPD. In another child who also had exacerbation of renal failure and was treated with HD for several months, deterioration of renal function led to ESRD. When the patient was transferred to CAPD, renal function remained unchanged but the degree of rehabilitation improved noticeably. All of the patients with ESRD on CADP are in good general condition, with serum creatinine levels ranging from 6.0 to 7.8 mg/dl.

In light of the observed improvement in renal function in the two above-mentioned children with CRF exacerbations treated with CAPD, it may be speculated that earlier introduction of CAPD in the latter child may also have been beneficial.

In adults with ESRA several advantages of CAPD over HD were noted: a similar incidence of peritonitis as in non-amyloidotic patients on CAPD, satisfactory quality of life, freedom of the circulatory stress of HD, better preservation of hemoglobin level, no need for heparinization and vascular access[2, 12, 13]. Good control of uremia suggests adequate dialysis and ultrafiltration across the peritoneum of amyloidotic children.

Besides the advantages of CAPD mentioned above, one cannot rule out the possibility that peritoneal dialysis removes some serum precursors of amyloid A protein (AA), which is the major component of different types of human secondary amyloidosis. This hypothesis requires further study.

The precursor of AA is serum amyloid A (SAA) of molecular weight of 84,000 to 200,000 daltons. SAA is probably a polymer of low-molecular-weight subunits called SAAL, bound to albumin or lipoproteins[13-15]. We hypothesize that elimination across the peritoneum of some medium-sized or low-molecular precursors of AA may limit the progression of amyloid deposition.

At the present time little experience has been reported with CAPD in amyloidotic children with ESRD and with CRF exacerbations. This treatment modality is very useful in children with ESRD, and its role in exacerbations of CRF has yet to be evaluated.

The hypothesis that CADP might improve the outcome of the disease is difficult to confirm because many other factors could also contribute to improved outcome with periodic exacerbations.

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NEUROLOGIC FINDINGS OF VITAMIN B_{12} DEFICIENCY: PRESENTATION OF 7 CASES*

*Ömer Kalaycı MD***, *Mualla Çetin MD****, *Birgül Kırel MD***
*Emire Özdirim MD*****, *Sevgi Yetgin MD*****, *Sabiha Aysun MD*****
*Aytemiz Gürgey MD*****

SUMMARY: Kalaycı Ö, Çetin M, Kırel B, Özdirim E, Yetgin S, Aysun S, Gürgey A. (Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Neurologic findings of vitamin B_{12} deficiency: presentation of 7 cases. Turk J Pediatr 1996; 38: 67-72.

In this report, seven children, four males and three females, between the ages of five and 16 years with megaloblastic anemia and neuropsychiatric disorders are presented. Macrocytosis was identified in peripheral blood smears in all seven patients. Serum B_{12} levels were markedly reduced in four and were at the lower limit of normal in three patients. The Schilling test showed that B_{12} deficiency was due to specific cobalamin malabsorption in five and to inadequate dietary intake in two patients. Both neurological and hematological findings returned to normal after B_{12} replacement. This study shows that B_{12} deficiency should be considered in the differential diagnosis of neuropsychiatric disorders in children, including those with nonvegetarian habits, and that such patients should undergo a thorough hematological evaluation. *Key words: B_{12} deficiency, megaloblastic anemia, neurological disorders.*

Neuropsychiatric disorders are a well recognized aspect of cobalamin deficiency and may occur even in the absence of anemia, especially in adulthood[1,2]. However, neurological findings are considered a late manifestation of the disease, and thus reports concerning children are rare. Most reports concern infants whose mothers are strict vegetarians[3-5]. Seven children followed at Hacettepe Children's Hospital with megaloblastic anemia due to specific cobalamin malabsorption or dietary deficiency, who also had neurological findings are presented. This report shows that cobalamin deficiency should be considered in the differential diagnosis of neuropathies and neuropsychiatric disorders in children even of non-vegetarian families, and that such patients should undergo a thorough hematological evaluation.

Material and Methods

Between 1978 and 1993, seven out of 56 patients diagnosed with megaloblastic anemia resulting from vitamin B_{12} (VB_{12}) deficiency had neurological symptoms on admission to Hacettepe Children's Hospital. Diagnosis of megaloblastic anemia

* From the Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara.
** Research Assistant in Pediatrics, Hacettepe University Faculty of Medicine.
*** Fellow in Pediatric Hematology, Hacettepe University Faculty of Medicine.
**** Professor of Pediatrics, Hacettepe University Faculty of Medicine.

was made on the basis of macrocytosis in the peripheral blood smear, megaloblastic changes in precursor cells in bone marrow and a decreased serum VB_{12} vlaue. All patients were treated with intramuscular VB_{12}, 100 µg daily for two weeks, every other day for another two weeks, and once monthly thereafter. The diagnostic criterion for Imerslund Grasbeck Syndrome (IGS) was specific VB_{12} malabsorption shown in the Schilling test in the absence of any malabsorption syndrome. A detailed dietary history was taken in all cases. The Schilling test was performed between three weeks and three months after initiation of therapy.

A summary of some of the clinical and laboratory findings is given in Tables I, II and III. In Case 3, from the past history it was learned that one year previously the patient had been evaluated for persistent proteinuria in the Department of Pediatric Nephrology of the same hospital; during that time a kidney biopsy was performed from the propositus, and pathological changes on light microscopy were compatible with Alport Syndrome. Five months prior to admission the patient developed ataxia. A day before admission, persistent projectile vomiting started. The family history revealed that she was the second product of a marriage between cousins. The mother had undergone transplantation due to chronic renal failure, while the father, one paternal aunt and one maternal uncle had hearing problems. Hematologic examination of the parents and siblings revealed no abnormalities. Hematological data and the Schilling test result are given in Table III.

Table I: Summary of Selected Clinical Features

Case	Age/Sex (years)	Complaints on Admission	Duration of Complaint (years)	Previous Treatment	Etiology	Recovery* Period (months)
1	12/M	Weakness	9	Blood trans.	IGS	2
2**	15/M	Pallor, weakness	4	Oral iron Blood trans.	IGS	2
3	5/F	Vomiting, gait abnormalities	2	Oral iron	IGS + Alport's Syndrome	3
4	13/M	Tingling in hands and feet	7	Blood trans.	IGS	3
5**	16/M	Pallor	5	Oral iron Folic acid, Blood trans.	IGS	6
6	15/F	Ataxic gait Tingling in lower extremities	6 month	—	Dietary VB_{12} def.	2***
7	12/F	Pallor, weakness	10	—	Dietary VB_{12} def.	1 week

* Neurological findings.
** Two patients were siblings.
*** Still on therapy at the time of submission.
trans : transfusion, IGS : Imerslund-Grasbeck Syndrome, def : deficiency.

Table II: Physical and Neurological Findings of Patients

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Physical Findings							
Pallor	+	+	+	+	+	−	+
Growth ret.	−	−	−	−	−	−	+
Glossitis	+	+	−	+	+	+	−
Neurologic Symptoms and Findings							
Hyperesthesia	+	−	−	−	+	+	−
Tremor	+	−	−	−	−	−	−
Muscular pain	+	−	−	−	−	−	−
Basinski	+	−	−	−	+	−	−
Clonus	+	−	−	−	−	−	−
Memory loss	−	+	−	−	+	−	−
Diminished Vibration sense	−	−	−	+	+	+	−
Diminished position sense	−	−	−	+	−	+	−
Ataxia	−	−	+	−	−	+	−
Double vision	−	−	−	−	−	−	+
Agitation	−	−	−	−	−	−	+
Hallucinations	−	−	−	−	−	−	+
Paresthesia of the hands and feet	−	−	−	+	−	−	−
DTR*	I	N	N	N	I	I	N

* DTR: deep tendon reflex, N: normal, I: increased.

Case 7 was diagnosed with megaloblastic anemia at the age of seven years. Her past history revealed that pallor was first noted when she was two years old but no medical advice was sought. The patient was treated with VB12 and discharged from the hospital. At the age of 12 years this patient came to our clinic with severe megaloblastic anemia and she complained of double vision which was followed immediately by a hard-to-control agitation and visual hallucinations without a gross motor deficit. From the history it was learned that the patient had discontinued VB_{12} after discharge and had not received any therapy during the past five years.

Table III: Selected Laboratory Findings of Patients

	Case						
	1	2	3	4	5	6	7
Hb (g/dl)	4.8 (11.3)	6 (12.9)	7 (12.6)	4.2 (12)	8.2 (13.2)	10.5 (13.4)	3.5 (12.8)
Htc (%)	11 (33)	20 (37)	21 (37)	13 (36)	26 (38)	31 (41)	9 (36)
Rct (%)	1 [12.6][b]	0.4 [14]	0.6 [8.2]	1 [11]	0.4 [3.4]	0.2 [8]	4.6 [15.6]
Leukocyte (/mm^3)	2400 (5200)	3500 (4200)	3000 (5200)	2800 (5600)	4000 (4800)	5200 (5600)	4800 (5200)
Platelet (/mm^3)	340.000	220.000	200.000	310.000	320.000	330.000	91.000
MCV (fl)	95 (81.4)	117 (83.2)	125 (82)	104 (84)	115 (86.2)	129.3 (86)	103.2 (83.2)
Vit B_{12} (pg/ml)	42	258	225	42	213	80	< 20
Folic acid (ng/ml)	8.4	7.49	8.5	4.95	8.6	9.1	8.11
58Co (%)	1	5.8	0.6	4	5.4	21	12.4
57 Co + IF (%)[c]	0	5.3	0.8	6.7	5.3	21	14
Serum iron	ND	258	ND	ND	322	132	32
Iron binding capacity	ND	242	ND	ND	271	275	275
Ferritin	ND	257.2	ND	ND	198	40	ND
Proteinuria	–	–	+	+	–	–	–
D - Xylose	N	N	N	N	N	ND	ND
Methylmalonic aciduria	–	–	+	–	–	+	–
Serum IgA	ND	D	N	ND	N	N	N
EMG	N	ND	ND	ND	ND	N	ND

a : Numbers in parentheses are values obtained two months after treatment.
b : Numbers in brackets are the maximum of reticulocyte counts on the third day of treatment.
c : Vitamin B_{12} - bound intrinsic factor.
ND : Not determined, D : Decreased, N : Normal, EMG : Electromyography.

Discussion

In this report all seven cases with bone marrow smears typical of megaloblastic anemia responded promptly, both hematologically and neurologically, to VB_{12} replacement. In Cases 1 through 5, the results of the Schilling test showed defective absorption of VB_{12} that cannot be corrected by the addition of intrinsic factor, which is suggestive of Imerslund-Grasbeck syndrome in the absence of growth retardation and abnormal malabsorption tests. Proteinuria, another component of the syndrome in over 90 percent of cases[6-8] was detectable in two of our patients (Cases 3 and 4). Since Case 3 had focal glomerulosclerosis and a family history of chronic renal failure and neural hearing loss, it was thought

that proteinuria might be a symptom of Alport's Syndrome. In Cases 6 and 7 the results of the Schilling tests were normal, indicating dietary deficiency of VB_{12}. It is obvious from the dietary history that the deficiency in both cases is most likely due to inadequate intake. In our study malabsorption syndromes due to VB_{12} deficiency were excluded by performing the Schilling test long after proper treatment.

All of the patients were started on VB_{12} therapy before learning their serum VB_{12} levels. Therefore, we were not able to restudy the serum VB_{12} level in patients whose initial serum VB_{12} level was near the normal level. Complete response to VB_{12} as far as anemia and neurological findings were concerned suggested to us that the diagnosis of VB_{12} deficiency was correct in these patients. Either laboratory error or an error in handling the blood specimens might be responsible for unexpectedly high initial VB_{12} values.

Megaloblastic anemia due to VB_{12} deficiency is rare in children. Although it is well established that B_{12} deficiency may present with neurological findings even without anemia, published reports usually concern cases in adulthood[1,2]. However, the age of onset of neurological findings varies. Infants born to vegetarian mothers are devoid of cobalaminstores at birth, and neurological findings are usually noted early in infancy[3-5] along with anemia. These findings suggest that the developing brain of early infancy is very sensitive to cobalamin deficiency. This deficiency, if unrecognized, may cause permanent neurologic damage in the infant. Neurological findings have also been reported as early as four to five years of age in a patient with specific B_{12} malabsorption[9]. The symptoms of subacute combined degeneration of the spinal cord due to VB_{12} deficiency often begin insidiously; decreased vibration and position sense are usually the first objective manifestations. Therefore in patients with these types of neurological abnormalities, VB_{12} deficiency should be considered.

In six of our patients, on the other hand, anemia preceded the onset of neurological findings by many years. In two patients with dietary deficiency, we do not know exactly when the inadequate intake started. In the cases with Imerslund-Grasbeck syndrome (Cases 1 through 5) cobalamin stores are theoretically depleted by the age of one year. However it took 12-16 years for the neurological symptoms to develop except for in Case 3. These observations may imply that individual differences contribute a great deal to the susceptibility of the brain to cobalamin deficiency, which may account for the difference in ages that neurological abnormalities first appear.

Magnetic resonance imaging and computerized tomography of the brain were available in Cases 5 and 7, and were normal in both cases. Salameh et al.[9], in their report concerning a male child aged four years and nine months, showed

the presence of cerebral atrophy on cranial computerized tomography which reversed completely with treatment. This may suggest that the brain may be affected to a greater extent by cobalamin deficiency in early childhood. In all of these cases, neurological symptoms were easily attributed to B_{12} deficiency because anemia was also evident. However, in childhood it is usually not well appreciated that cobalamin deficiency may present as a neurological syndrome with no hematological component, and thus many children with a true deficiency may go unnoticed. In this report Case 6 had only mild anemia and marked macrocytosis but obvious neurological symptoms, which was the main complaint that prompted the patient to seek medical attention. It is also noteworthy that dietary deficiency may also cause this syndrome in children with nonvegetarian dietary habits.

Since the condition can easily be diagnosed and treated, cobalamin deficiency should be considered a diagnostic possibility in all cases with unexplained neurological findings.

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MACRODACTYLY: REPORT OF EIGHT CASES OF A RARE ANOMALY*

*Naci Kostakoğlu MD***, Aycan Kayıkçıoğlu MD****, Tunç Şafak MD***
*Gürhan Özcan MD*****, Abdullah Keçik MD******, Güler Gürsu MD*******

SUMMARY: Kostakoğlu N, Kayıkçıoğlu A, Şafak T, Özcan G, Keçik A, Gürsu G. (Department of Plastic and Reconstructive Surgery, Hacettepe University Faculty of Medicine, Ankara, Turkey). Macrodactyly: report of eight cases of a rare anomaly. Turk J Pediatr 1996; 38: 73-79.

Macrodactyly or megalodactyly is a rare anomaly of the extremities. Neural factors are involved in the etiology. Presented here are eight cases which comprise five macrodactylous toes and three fingers. The mean age at first referral was 6.8 years. Six patients underwent resection of the proximal phalanges together with bulk reduction of the soft tissue mass. Only soft tissue reduction was performed in the remaining two patients. Skin necrosis was observed in two cases, one of which necessitated amputation at the proximal interphalangeal joint level. The functional outcome was evaluated as poor with limited range of motion and stiffness in the joints. As far as functional results are concerned, macrodactylous toes had a better prognosis than that of fingers.

It was concluded that none of the available methods as yet gives ideal functional and cosmetic results in macrodactyly. *Key words: macrodactyly, megalodactyly.*

Macrodactyly is overgrowth of the toes and fingers. Local gigantism, megalodactylia, megalodactilism, digital gigantism, macrodystrophia lipomatosa and localized hypertrophy have been used as synonyms for macrodactyly[1-5]. It is the least common congenital anomaly of the extremities, comprising 0.9 percent of the total number of reported cases in the literature[4, 5].

In many cases macrodactyly may be noted at the time of birth, whereas in some others abnormal growth appears soon after birth and often reaches gross proportions and constitutes a severe physical and psychological handicap. It is not always symmetrical. The finger or toe may tend to deviate toward the healthy side in cases where only one side of the finger becomes excessively hypertrophic. The etiology remains unexplained, with males affected more often, and association with other anomalies and family history is rare[1-5].

* From the Department of Plastic and Reconstructive Surgery, Hacettepe University Faculty of Medicine, Ankara.

** Assistant Professor of Plastic and Reconstructive Surgery, Hacettepe University Faculty of Medicine.

*** Research Assistant in Plastic and Reconstructive Surgery, Hacettepe University Faculty of Medicine.

**** Associate Professor of Plastic and Reconstructive Surgery, Hacettepe University Faculty of Medicine.

***** Professor of Plastic and Reconstructive Surgery, Hacettepe University Faculty of Medicine.

In true macrodactyly, all components of a digit are enlarged. It must be distinguished from other pathologies resulting in enlarged digits such as hemangiomas, arteriovenous malformations, congenital lymphedema and lipomas (Table I)[4, 5].

Table I: Other Pathologies Resulting in Enlarged Digits

Hemangiomas
Arteriovenous malformations
Congenital lymphedema
Lipomas
Multiple enchondromatosis with hemangiomas
Klippel-Trenaunay-Weber syndrome
Osteoid osteoma
Melorheostosis

In this article, eight cases of macrodactyly are presented and a comparison of results is made by reviewing the literature.

Material and Methods

Between 1965 and 1994, eight cases of macrodactyly were treated in our clinic. During this period, a total of 650 extremity anomalies were examined. In our series, macrodactyly consisted of 1.23 percent of these cases.

The age of the patients ranged from one to 25 years; five were female and three male. The patients all described the pathology as being present since birth, and all were operated on after their first referral to our clinic. The mean age at operation was 6.8 years.

Results

The patients are listed in Table II. In five of the patients the foot was the site of the anomaly, while in the remaining three the hand was affected.

Table II: List of Patients

Age of First Operation	Sex	Site	Digit	Assoc. Anomaly	Family History	Consanguinity
5	F	RF	2-3	–	–	–
3	F	LF	2	–	–	–
25	M	LF	4-5	–	–	–
2.5	F	LF	2-3	–	–	–
13	F	RH	3	–	–	–
1	M	LH	4	–	–	+
1	M	RH	3-4	+	–	+
4	F	RF	1-2	–	–	–

RF: right foot. LF: left foot.
RH: right hand. LH: left hand.

There was no positive family history in any of the patients. However, in two cases the parents were first and second degree relatives.

In one case, incomplete syndactyly of the long and ring fingers accompanied the macrodactyly (Figs. 1-4). Five out of eight patients had two digits involved, whereas in the remaining three only one digit was involved. The second and third rays were the most commonly affected digits.

The digital nerves were wound to be hypertrophic in all cases, one of which had hypertrophy of the soft tissues extending proximally to the palmar aspect of the hand; on exploration this was found to be due to hypertrophy of the median nerve starting from the entrance of the carpal tunnel (Fig. 5).

In five cases, partial resection of the proximal phalanges was performed together with reduction of soft tissue. Two cases underwent multiple reductions of soft tissue mass only. One had undergone amputation of the second ray of the foot by orthopedists at an early age, and underwent soft tissue resections in our clinic.

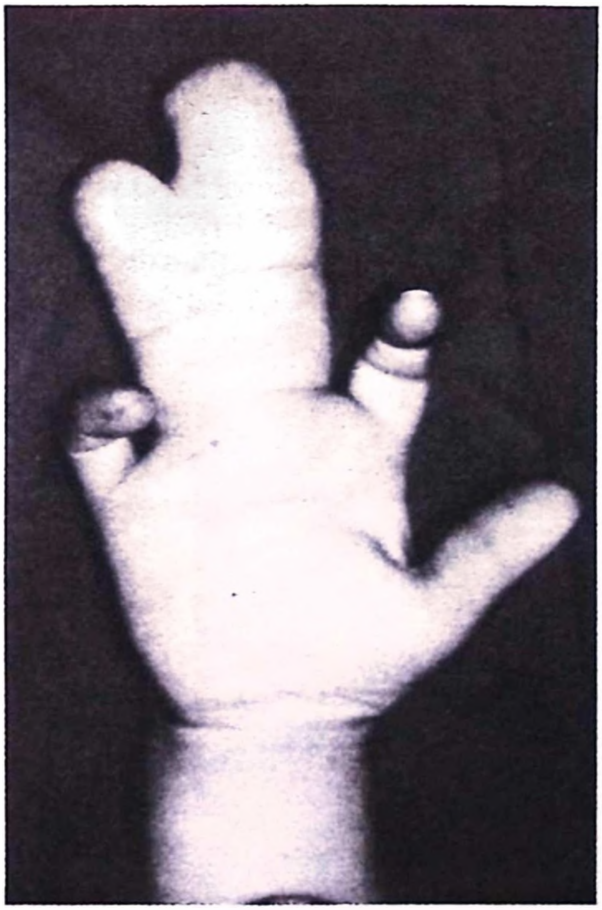

Fig. 1: Palmar view of third and fourth macrodactylous fingers together with incomplete syndactyly.

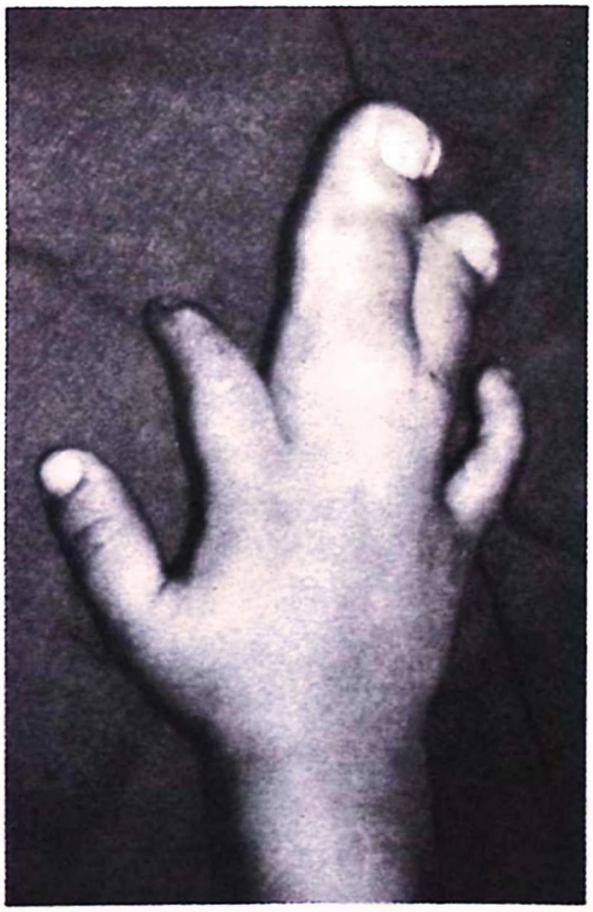

Fig. 2: Dorsal view of the same patient

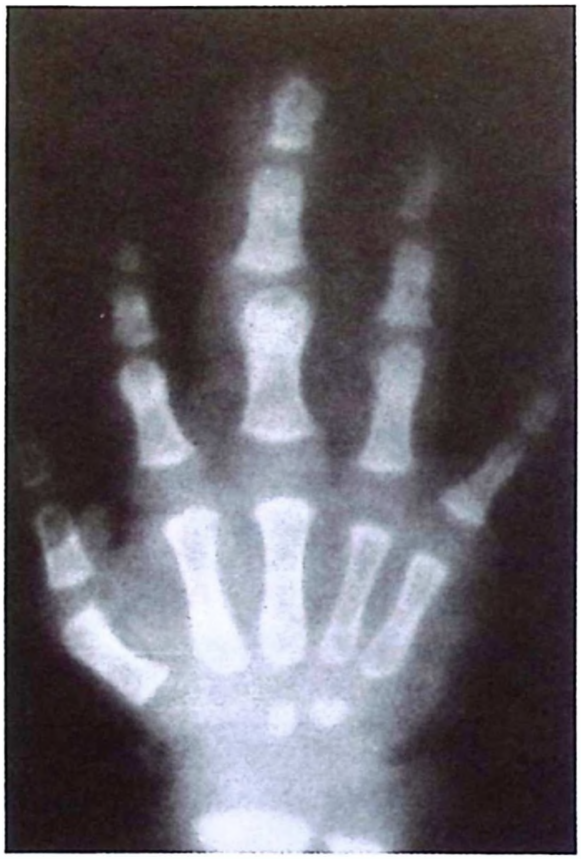

Fig. 3: X-ray of the macrodactylous hand.

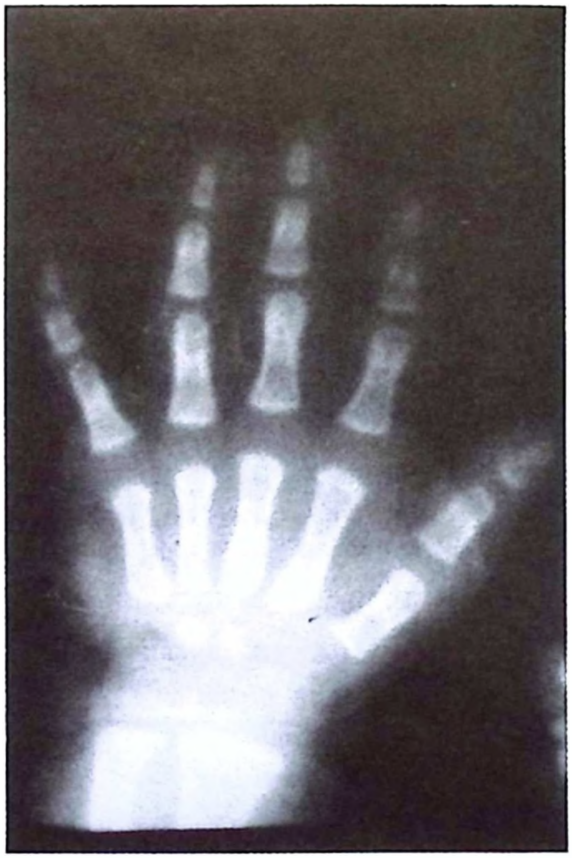

Fig. 4: X-ray of the normal hand of the same patient.

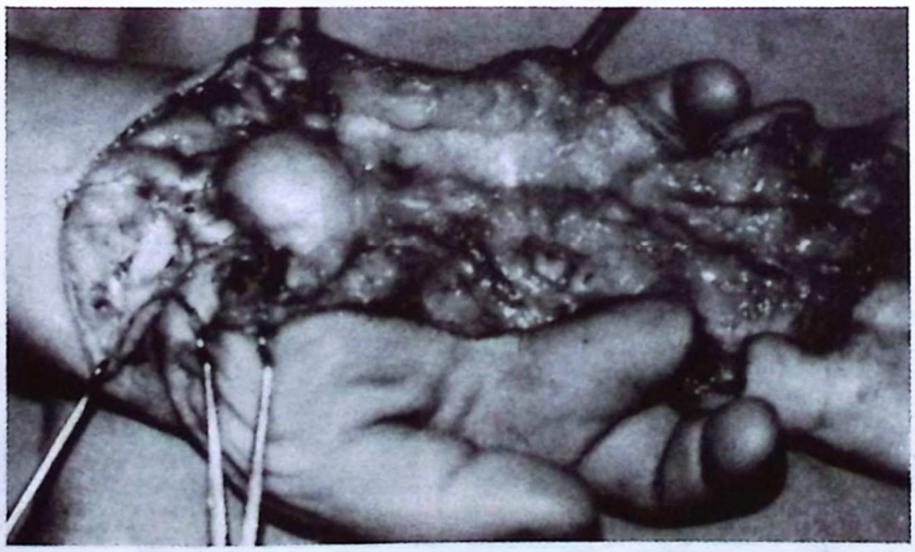

Fig. 5: Palmar soft tissue mass revealed to be a median nerve enlargement.

In two patients the postoperative course was complicated by necrosis of skin flaps. Supervening infection in one of these cases necessitated amputation of the long finger at the proximal interphalangeal (PIP) level. No further therapy was necessary in the other patient.

The functional outcome in macrodactylous fingers was poor, with limited range of motion and stiff joints which were of great concern in the upper extremity. In the foot this did not seem to be a problem since motion of the toes was rarely a matter of concern for the patient. Nearly all cases sought treatment mainly for cosmetic reasons; however, only two patients were satisfied with the final result, both of whom had macrodactylous toes. The remaining patients were neither satisfied nor wanted any more treatment.

Discussion

More than 300 fingers and 60 toes with macrodactyly have been reported[4]. Ninety-five percent of the cases were found to occur unilaterally[4]. No predilection for the right or left extremity was observed[3, 4]. The index finger was the most commonly affected finger, followed by the long finger, thumb, ring and little fingers in decreasing frequency. Involvement of multiple digits was found to occur more often than a single digit. Also, two digits were more frequently affected than three digits. The thumb and index finger, or the index and long finger, were the most commonly encountered combinations. Syndactyly was seen in 10 percent of cases[4].

In our series, macrodactyly of the toes was more common than the fingers. This is in contrast to the reports in the literature. A random refferral pattern of congenital anomalies in our country seems to be the responsible factor for this difference. We have also encountered no predilection for the right or left extremity.

The long and ring fingers and the second toe were the most commonly involved digits, and the finding that two digits were more commonly affected than three digits was also confirmed in our patients. The predominance of macrodactyly of the long and ring fingers in our series is in accordance with the report of Barsky[6]. However, Dobyns et al.[4] found the index finger to be the most commonly affected digit.

None of our patients had a family history of macrodactyly nor any other extremity anomalies. However, in two patients the parents were blood relatives. Macrodactyly is claimed not to be inherited, while association with other syndromes is reported to be a causative factor in inheritance as an autosomal dominant trait. Marriage between blood relatives is common in our country, and our two patients with consanguinity must have been incidental.

Treatment should be planned on an individual basis. Flatt[5] states that there is no correct age at which surgery should be started. Tsuge[1] advocates the inhibition

of finger growth when hypertrophy is not too marked, while shortening or reduction in size should be done after marked macrodactyly has developed.

In our series, the age at first referral ranged from one to 25 years. All patients but two were seen before five years of age. According to our experience, the disfigurement and malfunction caused by macrodactyly urges families to seek early intervention. Excluding the two late referrals, it seems that macrodactyly of the finger causes earlier awareness than macrodactyly of the toe.

A variety of operative strategies have been reported[1-6]. Dobyns et al.[4] recommends bulk reduction without any shortening of the bone for the young child. Tsuge[1] on the other hand reduces the length of the macrodactylous finger by excising the volar part of the distal phalanx and the dorsal portion of the middle phalanx, thereby the dorsal part of the distal phalanx and nail are recessed to fit the middle phalanx. If further shortening of the digit is required, he recommends excision of the MP joint.

When the size of the involved digit reaches the size of the same digit of the patient's parent of the same sex, epiphyseal arrest at the proximal end of each phalanx is advocated[5]. However, epiphysiodesis is reported to be extremely difficult and frustrating[4].

Our treatment policy was bulk reduction for the very early cases and addition of proximal phalangeal reduction in the older patients, which is a modification of the method for reduction of the thumb described by Millesi[7].

Tsuge[1] postulates that neural stimulation causes disproportionate growth of the finger. He therefore advocates stripping the branches of the digital nerves from the digital nerve trunk. The true incidence of median and ulnar nerve enlargement is unknown[1,4,8]. We have observed hypertrophy of the median nerve in one of our cases, which presented itself as a soft tissue mass in the palm. There is agreement in the literature that stiffening of the joint and degeneration of the bone results in a nearly motionless finger in most cases, and sometimes amputation is indicated for a huge digit that interferes with function of the rest of the hand[1,4,5].

Five of the macrodactylous digits in our series were located in the foot. Therefore, little concern was given to the functional outcome after surgery. In those cases with macrodactyly of the fingers, functional and aesthetic results were generally poor, and all patients required multiple operations. Skin necrosis was a serious problem in two cases, one of which necessitated amputation at the PIP level owing to supervening infection.

In conclusion, macrodactyly remains a challenge for the hand surgeon, and the perfect solution to the problem is yet to be found.

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LOW EXPRESSION OF T-CELL RECEPTOR-CD3 COMPLEX: A CASE WITH A CLINICAL PRESENTATION RESEMBLING HUMORAL IMMUNODEFICIENCY*

*Özden Sanal MD***, *Leman Yel MD****, *Fügen Ersoy MD***
*İlhan Tezcan MD*****, *A. İzzet Berkel MD***

SUMMARY: Sanal Ö, Yel L, Ersoy F, Tezcan İ, Berkel Aİ. (Immunology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Low expression of T-cell receptor-CD3 complex: a case with a clinical presentation resembling humoral immunodeficiency. Turk J Pediatr 1996; 38: 81-84.

Low expression of T-cell receptor-CD3 (TCR-CD3) complex, a rare cause of combined immunodeficiency, has only recently begun to be recognized. Here we report a four-year-old boy who has defective TCR-CD3 complex expression presenting with recurrent chest infections and pulmonary symptoms implying bronchial asthma. In our opinion, this entity should be borne in mind as the possible underlying defect in children with combined immunodeficiency having signs and symptoms of humoral immunodeficiency.
Key words: severe combined immunodeficiency, T-cell receptor, CD3 complex.

Combined immunodeficiencies are a group of diseases characterized clinically and immunologically by defects in both T and B lymphocytes. The clinical presentation usually includes failure to thrive and unusually persistent and potentially lethal infections with low virulence opportunistic organisms in infancy. However, the underlying T-cell defect is heterogeneous, leading to a wide spectrum of symptomatology[1-6]. Low expression of T-cell receptor-CD3 (TCR-CD3) complex, a rare cause of combined immunodeficiency, has only recently begun to be recognized and has been described in only three children, of whom two had clinical problems[2,4].

Here, we report a four-year-old male patient who had defective expression of the TCR-CD3 complex, presenting with recurrent chest infections and pulmonary symptoms implying bronchial asthma.

Case Report

A four-year-old boy was referred to the Immunology Unit, Hacettepe University Children's Hospital, because of recurrent pulmonary infections. He has born after and uncomplicated term pregnancy with a body weight of 3000 g as the eighth

* From the Immunology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara.

** Professor of Pediatrics, Hacettepe University Faculty of Medicine.

*** Pediatrician, Hacettepe University Faculty of Medicine.

**** Associate Professor of Pediatrics, Hacettepe University Faculty of Medicine.

child of first-degree consanguineous parents. Frequent cough and wheezing usually with fever had been the major complaints since the age of six months. Chest infections had been diagnosed and treated with various antibiotics on more than 10 occasions, twice requiring hospitalization. Two months before he was referred, bronchial asthma was diagnosed and he was put on ketotifen and cromolyn sodium, resulting in amelioration. In addition to pulmonary symptoms, he had experienced urinary tract infections. BCG (Bacille Calmette Guerin), DPT-OPV (Diphteria, pertussis, tetanus, oral polio vaccine), and measles vaccinations had been administered without any complications. The developmental stages were within normal limits. He had recovered from chicken pox spontaneously at two years of age. Three of his siblings had died: the first sibling (female) of chicken pox at the age of 18 months, the third sibling (female) of measles at the age of 15 months, and the fourth (female) probably of leukemia (according to the history given by the family) at the age of 11 months. The remaining one male and three female siblings were healthy. There was no history of frequent infections in the family.

On physical examination, the patient weighed 14 kg (10^{th} - 25^{th} percentile) and measured 96 cm (10^{th} - 25^{th} percentile). He had a refraction error of the eyes. The rest of the systemic findings were unremarkable with neither dysmorphic features nor bony abnormalities.

Table I: Laboratory Data of the Patient[1]

Hemoglobin		12 g/dl
White blood cell count		6100/mm3
Absolute neutrophil count		3782/mm3
Absolute lymphocyte count		2108/mm3 (2900-5100)
Serum IgG		10.6 g/L (7.45-18.04 g/L)
Serum IgM		0.76 g/L (0.52-2.97 g/L)
Serum IgA		0.42 g/L (0.44-2.44 g/L)
Isohemagglutinin (anti-B) (Blood group A Rh+)		1/64
Antibody to poliovirus (1)		1/28
(2)		1/256
(3)		1/16
Anti-microsomal antibody		1/100
Anti-thyroglobulin antibody		1/160
C3		59.5 mg/dl
C4		30.6 mg/dl
CH50		31 IU/ml
Delayed type hypersensitivity	(PHA)	(+)*
	(Candida)	(+)
	(ppd)	(+)
Lymphocyte subpopulations	(CD3)**	30% (62-69)
	(CD4)	22% (30-40)
	(CD8)	19% (25-32)
	(CD19)	25% (21-28)
In vitro lymphocyte transformation to***		
	(PHA)	755 cpm (control 94, 842 cpm)
	(Con A)	556 cpm (control 36, 794 cpm)
	(medium)	350 cpm (control 872 cpm)

Numbers in parentheses indicate age-related normal values.
PHA : Phytohemagglutinin.
Con : Concanavalin-A
ppd : Purified protein derivates.

* Induration of 4-5 mm.
** Fluorescence intensity was about 1/3 of normal (histogram obained by FACS analysis and with Leu-4 mAb).
*** Lymphocyte transformation to antigens could not be studied.

Some of the laboratory investigations are shown on Table I. T lymphocytes expressed CD3 at about one-third of normal fluorescence intensity. HLA typing was as follows: A2, A36, B27, B50, CW6, DR7, DR11, DQ2, DQ7.

Erythrocyte adenosine deaminase (ADA) activity was within normal limits (43.7 µmol uric acid/h/g Hb). The total eosinophil count was 200/mm^3, and bacteria and polymorphonuclear leukocytes were seen on the nasal smear. The chloride concentration in sweat was 10 mEq/L. X-ray disclosed chronic changes in the lung fields and maxillary sinusitis.

He was diagnosed as having combined immunodeficiency, and low expression of TCR-CD3 complex was suspected based on the slight lymphopenia, the diminished number and low fluorescence intensity of CD3$^+$ T lymphocytes, and the markedly defective in vitro lymphocyte transformation to mitogens. The diagnosis was kindly confirmed by further investigations performed by Dr. J. Vossen and Dr. M. van Tol, Department of Pediatrics, and Dr. F. Koning, Department of Immunohematology and Bloodbank, Leiden University Hospital, The Netherlands. Molecular studies of the patient and the family are currently in progress. Preliminary data strongly suggest the absence of CD3-γ chain protein.

Having been on intravenous immunoglobulin replacement therapy (400 mg/kg/month), the patient was well after eight months of follow-up at the outpatient clinic without having experienced recurrent infections.

Discussion

Combined immunodeficiencies are a group of heterogeneous, primary disorders with respect to clinical presentation as well as T and B lymphocyte functions[6]. In our patient who had laboratory findings consistent with T-cell immunodeficiency, adenosine deaminase deficiency, purine nucleoside phosphorylase deficiency, and Major Histocompatibility Complex (MHC) class II deficiency were excluded by the relevant laboratory tests. The relatively mild clinical presentation, the pattern of T-cell subsets, and the low fluorescence intensity of CD3 on T lymphocytes were compatible with the diagnosis of low expression of TCR-CD3 complex, which was included in the combined immunodeficiencies by the report of a WHO Scientific Group in 1992[6].

The recognition of foreign antigens by T lymphocytes is a crucial step in a normal immune response. T lymphocytes recognize antigens by means of a group of membrane proteins called the TCR-CD3 complex. The T-cell receptor α and β heterodimer binds antigen, and the Cd3-γ, CD3-δ, CD3-ε, CD3-ζ and CD3-η chains function in signal transduction to the cell nucleus to trigger T-cell response. Helper (CD4+) T-cells are induced to secrete factors that help B lymphocytes synthesize specific antibodies, and cytotoxic (CD8+) T-cells are stimulated to

lyse virally infected cells[1]. Therefore, a defect in the expression of or function of the TCR-CD3 complex would be expected to cause a combined immunodeficiency. To date, reports of two families with this disorder from two different centers have been published. The proband in the Spanish family reported presented with failure to thrive at the age of eleven months, and thereafter chronic anorexia, diarrhea and recurrent bronchopneumonia developed. The patient died because of viral pneumonia and severe autoimmune hemolytic anemia at the age of three years[2,5]. His male sibling had a relatively benign clinical presentation with asthmatic bronchitis and allergic rhinitis and was healthy at the age of 10 years at the latest report[2,3]. In the family described by the French group, a four-year-old boy presented with recurrent pneumonia and otitis media at two years of age[4,7]. Low expression of the TCR-CD3 complex in this patient was due to an abnormal CD3-ε subunit[8], while the defect in the two siblings was in the CD3-γ chain protein[3]. The clinical presentation of our patient was particularly similar to the patient in the second family. Our patient had recovered from chickenpox spontaneously and did not experience life-threatening infections, while his two female siblings who probably had the identical immunologic defect had died of chickenpox and measles. The difference in clinical severity is proposed to be due to redundancy of the immune system, and the encounter with environmental insults was also observed in the Spanish siblings[2].

Finally, we believe that low expression of TCR-CD3 complex should be borne in mind as the possible underlying defect in children presenting with signs and symptoms of a humoral immunological deficiency.

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GALACTOSIALIDOSIS IN TWO SIBLINGS*

*Aysel Yüce MD***, *Nurten Koçak MD****, *Guy T. Besley PhD*****

SUMMARY: Yüce A, Kocak N, Besley GT. (Gastroenterology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey, and Willink Biochemical Genetics Unit, Royal Manchester Children's Hospital, Manchester, United Kingdom). Galactosialidosis in two siblings. Turk J Pediatr 1986; 38: 85-89.

Galactosialidosis is a rare lysosomal storage disease associated with deficiencies of α-galactosidase and β-neurominidase. In this report, two siblings with galactosialidosis, resembling Niemann-Pick disease with the presence of foamy cells in multiple organs, splenomegaly and prominent hepatomegaly, are presented.

Galactosidase deficiency and an increased number of urinary sialic acid compounds were determined in these cases, and prenatal diagnosis was performed for their fourth sibling. Besides the presence of the typical clinical features, enzyme study is essential for the diagnosis of lysosomal storage disease and it facilitates in making the prenatal diagnosis.
Key words: lysosomal storage disease, galactosialidosis, α - galactosidase, β - neurominidase.

Galactosialidosis (GS) described by Goldberg et al.[1] is a lysosomal storage disease associated with decreased α-galactosidase and β-neurominidase activity due to lack of a protective protein. It is a well-established autosomal recessive disorder with several clinical types, such as early and late infantile and juvenile-adult forms, according to the age of onset and mortality. The symptoms include hepatosplenomegaly, severe edema, ascites during infancy, skeletal dysplasia, dysmorphism, ocular findings, neurological manifestations and mental retardation. The clinical diagnosis is supported by the presence of foamy cells in the bone marrow and multiple organs. But the definitive diagnosis requires urinary oligosaccharide chromatography followed by the appropriate enzyme studies[2-5].

Because of the rarity of this disease and the occurrence in four siblings, we report here in two siblings with GS diagnosed by enzyme studies. These cases appear to be the first cases reported from Turkey.

Case Reports

Case 1

A three-year-old girl was the first child of a first-degree consanguineous marriage. She was first seen with the complaints of abdominal distention and growth retardation. Her motor development was normal. On admission the physical

* From the Gastroenterology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, and Willink Biochemical Genetics Unit, Royal Manchester Children's Hospital, Manchester.

** Associate Professor of Pediatrics, Hacettepe University Faculty of Medicine.

*** Professor of Pediatrics, Hacettepe University Faculty of Medicine.

**** Top Grade Biochemist, Willink Biochemical Genetics Unit, Royal Manchester Children's Hospital.

examination revealed a well-looking child with a weight of 11 kg (< 5th percentile), a height of 89 cm (< 5th percentile) and head circumference 50 cm (75th percentile). She had mild mental retardation, coarse facial features, exophthalmic appearance, a short neck and depressed nasal bridge. Her liver was smooth and palpable eight cm and her spleen four cm below the costal margins respectively (Fig. 1).

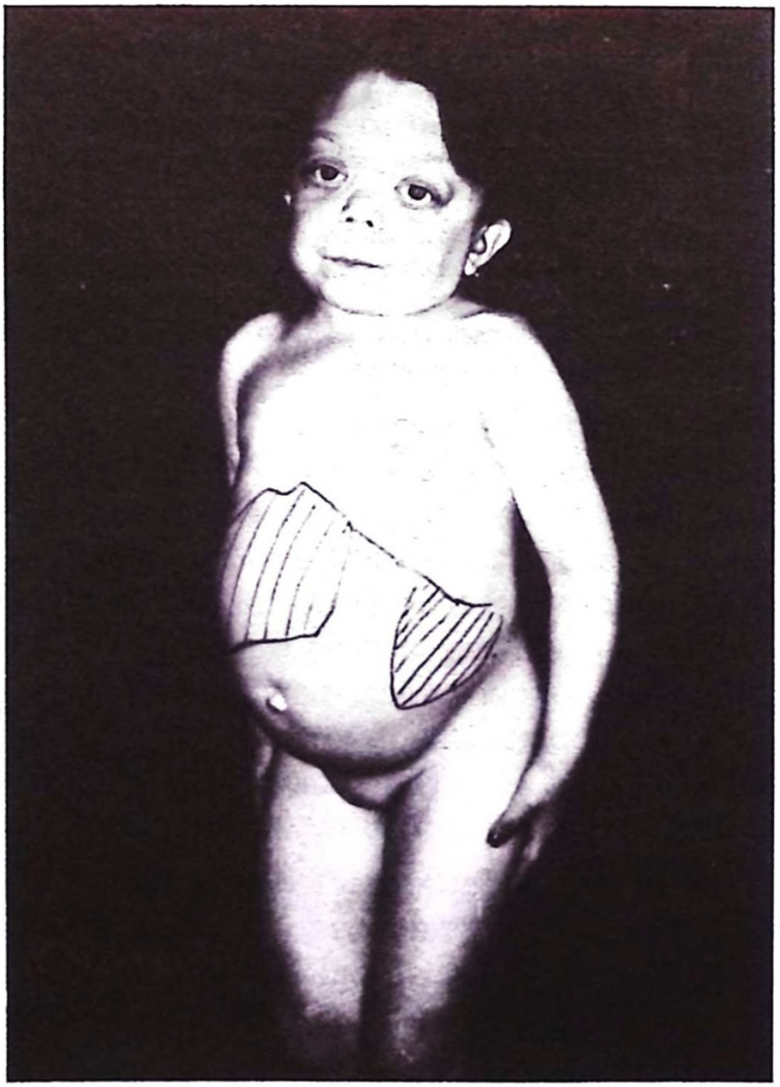

Fig. 1: The first case at 14 years of age. She had hepatosplenomegaly, coarse facial features, shot neck, macrocephaly and exophthalmic appearance.

The following laboratory data were within normal limits: complete blood counts, liver and renal function tests, serum triglyceride and cholesterol, urinary mucopolysaccharides, serum and urine amino acids and x-rays of the vertebrae. Bone marrow aspirate and liver biopsy disclosed foamy cells resembling those encountered in Niemann-Pick disease (Fig. 2). When the patient was admitted with pain in her right arm at nine years of age, a bone biopsy obtained from the right shoulder with a suspicion of osteomyelitis revealed the same type cells.

Sphingomyelinase activity in cultured skin fibroblasts and glucuronidase activity in leukocytes were normal. Leukocyte α-galactosidase was low (5% of control). In the urine, free sialic acid was 82.32 nmol/Omol Cr (control 20.4-37.1), and bound sialic acid was 281 nmol/Omol Cr (control 7.2-32.31). During follow-up the hepatosplenomegaly progressed, and palpebral edema and proteinuria were observed at the age of 13 years. Total serum proteins were 5.2 g/dl and albumin 2.6 g/dl. The patient died at home at the age of 15 years.

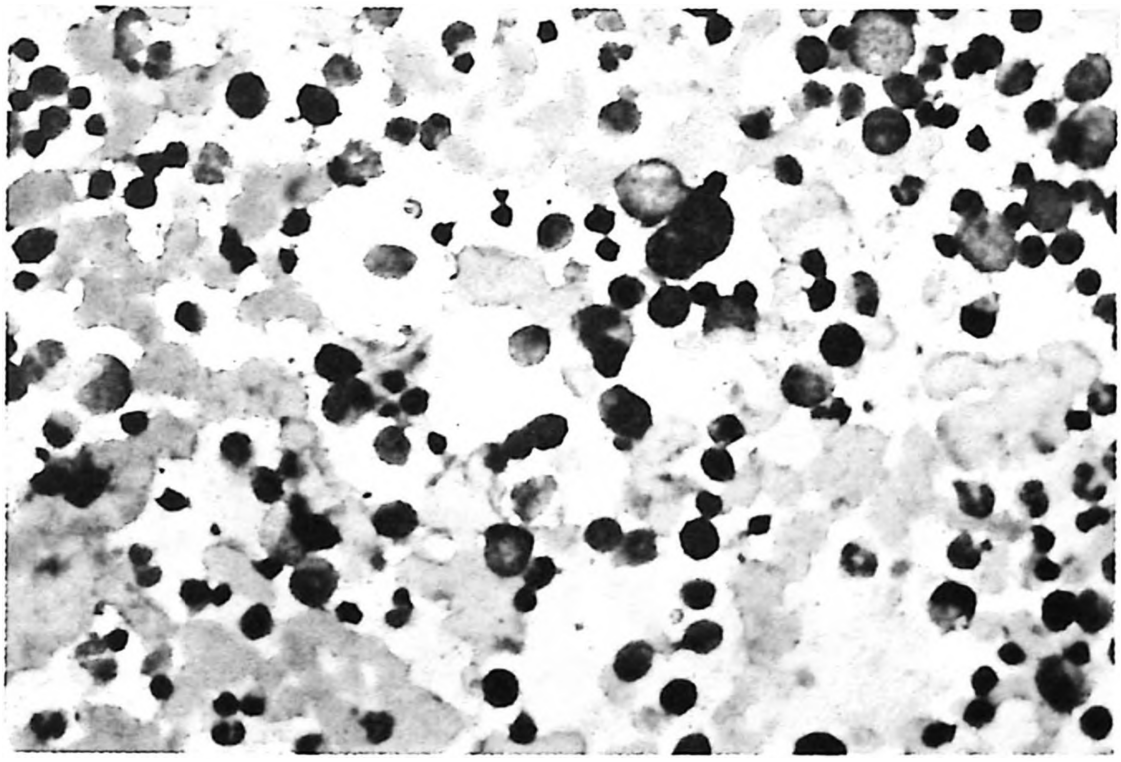

Fig. 2: Foamy cells resembling those seen in Niemann-Pick disease were present in the bone marrow.

Case 2

A three-year-old girl, the sister of the first case, was admitted to the hospital because of abdominal distention. Her weight was 13.5 kg (25^{th} - 50^{th} percentile). Her liver was smooth and palpable six cm and her spleen three cm below the costal margins, respectively. She had the same phenotype (Fig. 3) and laboratory findings of her elder sister. Sphingomyelinase and α-glucosidase activities were within normal limits. A deficiency of leukocyte α-galactosidase was found (5% of control). The urine contained increased amounts of free and bound sialic acids. During follow-up a 3/6 degree systolic murmur was heard along the left sternal border. Echocardiography indicated a thickening on the left mitral and aortic valves, as well as both mitral and aortic valve insufficiency. The patient is now 11 years old and has the same features.

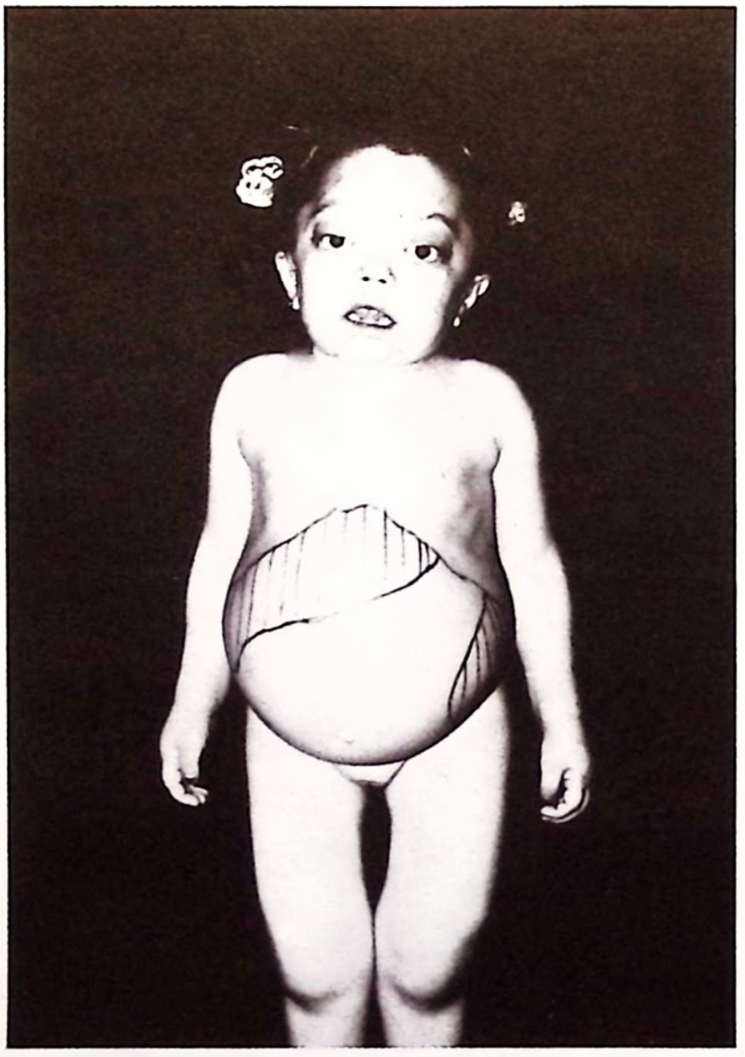

Fig. 3: Case 2 at 11 years of age. She presented with all the clinical features of galactosialidosis.

A third sister had died at two years of age following the development of abdominal distention, however no biochemical or necropsy studies had been done.

Prenatal diagnosis was performed for their fourth sibling. α-galactosidase and β-neurominidase deficiencies were found and the pregnancy was terminated[6].

Discussion

The clinical manifestations of GS result mainly from generalized sphingolipid storage and mimic GM_1 gangliosidosis. Foamy cells seen on bone marrow aspiration and multiple organs resemble Niemann-Pick disease[2].

The clinical presentations of our patients were suggestive of Niemann-Pick disease. But it was interesting that hepatomegaly in the two siblings was more

prominent than splenomegaly. The huge amounts of sialic acid compounds excreted in the urine as well as reduced α-galactosidase activity indicated that our cases belong biochemically to GS.

Miyashits et al.[7] classified this entity into three forms. The clinical features of the forms are highly heterogeneous, and intermediate forms are expected to be found. In fact these phenotypes may represent a continuous spectrum of phenotypes. Our patients appeared to fulfill some of the criteria of both late-infantile and adult forms of the disease.

Besides the classical features, endocardial and renal involvement are likely in GS[3, 8]. In the first case, proteinuria developed due to probable renal involvement. Unfortunately the renal findings could not be investigated. The second case had mitral and aortic insufficiency due to the cardiac component of the disease. Cardiac involvement, the most important clinical feature in management, has been reported in some cases of GS[8]. Patients with GS should be evaluated for both cardiac and renal findings. There is no effective therapy for GS; the management is based on clinical findings.

Studies on the molecular background of this autosomal recessive entity are continuing. The occurrence of the disease in all four children of this family is interesting, suggesting a different mode of inheritance. These cases also point to the importance of enzymatic assay in the diagnosis of lysosomal storage diseases. Enzymatic assay is also essential for accurate genetic counseling and facilitates in making a prenatal diagnosis in subsequent pregnancies.

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TREATMENT OF HEMOPHILIC PSEUDOTUMOR WITH LOW – DOSE RADIOTHERAPY *

*Namık Özbek MD***, *Metin Ünsal MD****, *Abdurrahman Kara MD***
*Fatma Gümrük MD*****, *Aytemiz Gürgey MD******

SUMMARY: Özbek N, Ünsal M, Kara A, Gümrük F, Gürgey A. (Hematology Unit, Department of Pediatrics, and the Department of Radiology, Hacettepe University Faculty of Medicine, Ankara, Turkey). Treatment of hemophilic pseudotumor with low-dose radiotherapy. Turk J Pediatr 1996; 38: 91-94.

Hemophilic pseudotumor is one of the most serious complications of hemophilia and is usually treated with extensive surgery. A new treatment approach is radiotherapy. Patients with long-bone pseudotumors are usually treated with high doses of radiotherapy greater than 1500 cGy. We treated a 13-year-old hemophilic boy who had a pseudotumor of the tibia with low-dose radiotherapy (600 cGy). There was no complication during the two-and-a-half-year follow-up. Improvement of both the clinical and radiological status of the patient was noteworthy. We would like to suggest the use of low-dose radiotherapy in patients with hemophilic pseudotumors.
Key words: hemophilia, pseudotumor, external radiotherapy.

Hemophilic pseudotumor is one of the most serious complications of hemophilia. It was first described by Starker[1] in 1918 in the femur of a 14-year-old boy with hemophilia. It is sometimes confused with various malignant and benign bone diseases. The lower extremities and pelvis are most frequently affected, but almost all sites may be involved[2]. Recurrent hemorrhage into an encapsulated hematoma causes destruction and finally cyst formation in the bone. Increased levels of Factor VIII (F-VIII) inhibitor may render F-VIII supplementation ineffective and surgery impossible[3]. In some cases pseudotumors can become large enough to threaten the patient's life.

Hemophilic pseudotumors are usually resistant to medical treatment. Radical surgical procedures such as amputation are often needed in these cases[4]. However, in recent articles it has been reported that radiotherapy and/or F-VIII supplementation were successfully used in some patients[5]. The present report describe a patient who presented with a pseudotumor in the tibia and was treated with a lower dose of radiotherapy.

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* From the Hematology Unit, Department of Pediatrics, and the Department of Radiology, Hacettepe University Faculty of Medicine, Ankara.

** Pediatrician and Fellow in Pediatric Hematology, Hacettepe University Faculty of Medicine.

*** Professor of Radiology, Hacettepe University Faculty of Medicine.

**** Pediatric Hematologist, Hacettepe University Faculty of Medicine.

***** Professor of Pediatrics and Pediatric Hematologist, Hacettepe University Faculty of Medicine.

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Case Report

A 13-year-old male patient who had been diagnosed with severe hemophilia-A at the age of three months (F-VIII level 1.2 U/dl) was admitted to the hospital with hemarthrosis of the left knee which developed after blunt trauma to that region. Fresh frozen plasma three times per day was transfused for a week to the patient for the treatment of hemarthrosis. Neither pain relief nor reduction in the size of the knee was achieved during the course of treatment. Radiography of the left knee showed a lytic lesion in the tibial tubercle. The continuity of the bone cortex, especially in the anterior part, was disturbed. There were radiolucent cysts with a septal formation in the proximal one-third of the tibia which was diagnosed as a hemophilic pseudotumor (Fig. 1). Factor VIII inhibitor was negative at that time. Since replacement therapy was ineffective, the patient was given a total of 600 cGy of Cobalt 60 photons in four fractions (150 cGy/day) to the left knee for four consecutive days. He was able to walk without pain and the knee swelling was resolved a week after the beginning of radiotherapy. The last physical examination revealed neither deformity nor disturbance of growth. The lytic lesion was significantly diminished with new periostal lamellary bone formation on the radiograms obtained 1.5 and 2.5 years after radiotherapy (Figs. 2 and 3). There was a minimal defect in the tubulation of bone.

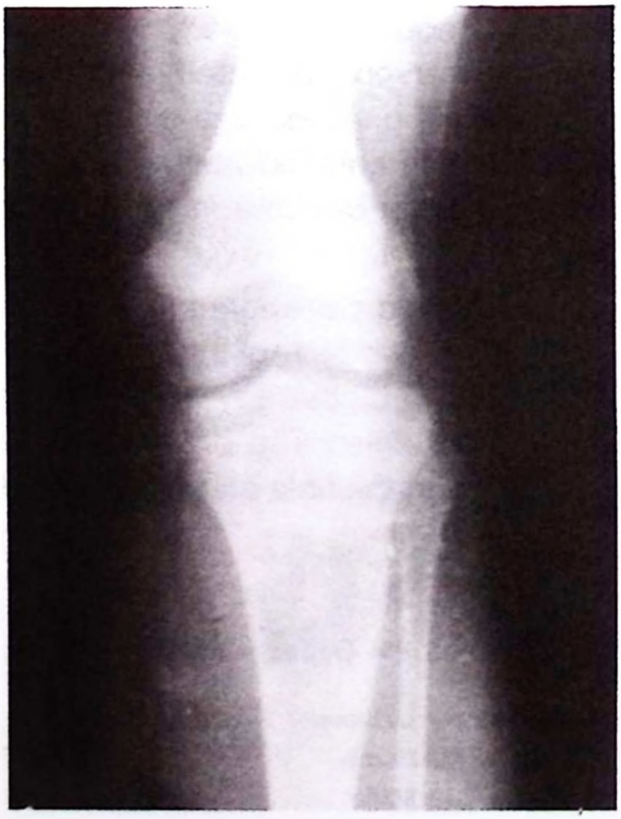

Fig. 1: Posteroanterior view of the left knee before therapy.

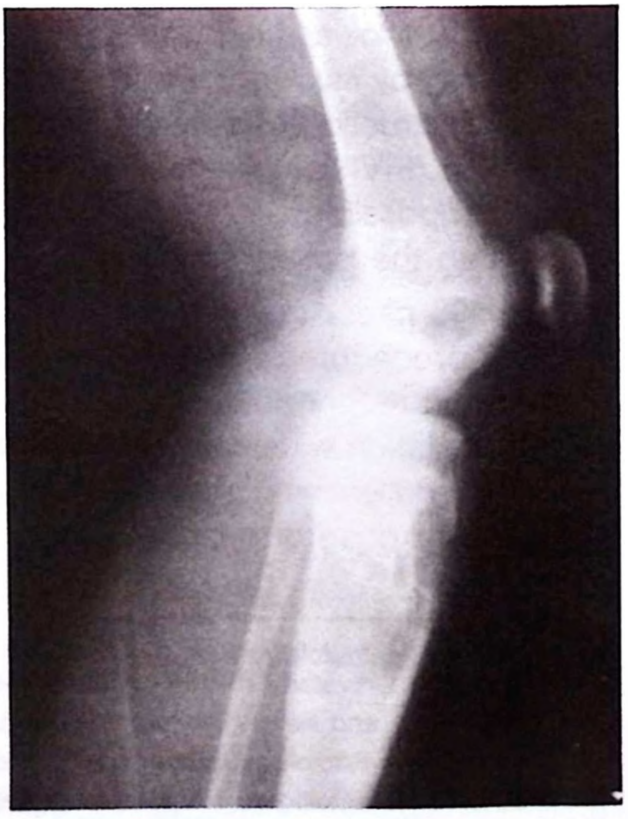

Fig. 2: Lateral view of the left knee one-and-a-half years after radiotherapy.

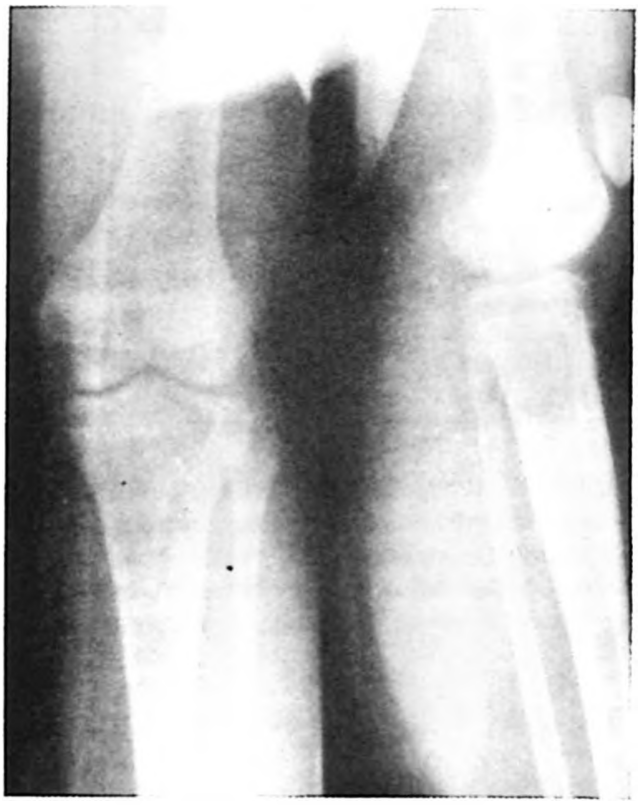

Fig. 3: Lateral and posteroanterior view of the left knee two-and-a-half years after radiotherapy.

Discussion

Replacement therapy has been effective in small-sized pseudotumors. However, large lesions are usually treated with surgical intervention. Bleeding episodes may be impossible to control with replacement therapy in patients with high titers of inhibitors to F-VIII or factor IX. Therefore, some investigators have advocated the use of radiotherapy. Despite the fact that F-VIII inhibitor was negative in our patient, we could not achieve satisfactory results with appropriate replacement therapy. In the literature it has been reported that patients with long-bone pseudotumors were usually treated with high doses of radiotherapy up to 1500 cGy. In a recent article, Castaneda et al.[3] reported good results with a lower dose of radiotherapy in a mandibular pseudotumor, but they used higher doses up to 1500 cGy for long-bone pseudotumors. Our patient was an adolescent boy with accelerating growth that could be affected by high doses of radiotherapy up to 10 Gy. Therefore, we decided to treat our patient with low-dose radiotherapy. As soon as the therapy was completed, the pain was alleviated and the patient was able to walk. It was noteworthy that he did not develop any symptom or hemarthrosis in his left knee within two-and-a-half years following radiotherapy. His last physical examination showed that growth of the tibia was not affected. He is now able to walk with a slight limp.

We would like to suggest the use of a lower dose of radiotherapy in patients with hemophilic pseudotumors.

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MULTIPLE INTRACRANIAL TUBERCULOMAS IN A CHILD *

*Güliz Erdem MD***, *Mehmet Ceyhan MD****, *Zafer Ecevit MD****
*Güler Kanra MD*****, *Elif Erkul MD***

SUMMARY: Erdem G, Ceyhan M, Ecevit Z, Kanra G, Erkul E. (Infectious Diseases Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Multiple intracranial tuberculomas in a child. Turk J Pediatr 1986; 38: 95-99.

Intracranial tuberculomas continue to be a serious complication of central nervous system tuberculosis. Tuberculomas are conglomerates of tubercles resulting from hematogenous spread of tuberculous infection. Modern neuroimaging studies such as magnetic resonance imaging and molecular biologic techniques such as polymerase chain reaction are helpful in the diagnosis of central nervous system tuberculosis and tuberculomas. We report a boy with multiple intracranial tuberculomas diagnosed and treated with the aids of magnetic resonance and polymerase chain reaction techniques.
Key words: intracranial tuberculoma, gadolinium-DTPA-enhanced magnetic resonance imaging, polymerase chain reaction.

Tuberculosis is still a major cause of serious illness in the developing world. Tuberculosis of the central nervous system (CNS), although uncommon in children, continues to be a severe, life-threatening form of tuberculosis. Neurologic sequelae are common and the mortality rate ranges from 15 to 35 percent. Tuberculomas are the most common parenchymal form of CNS tuberculosis.

We report a boy with multiple intracranial tuberculomas diagnosed with the aid of gadolinium-DTPA-enhanced magnetic resonance (MR) studies.

Case Report

A 14-year-old boy was referred from a local hospital with a one-month history of double vision and ptosis. the had an eight-month history of progressively severe headache. He also had generalized convulsions with vomiting and fever beginning six months previously. His mother had a history of tuberculosis diagnosed and treated 2.4 years prior; the family history was otherwise unremarkable.

On physical examination his height and weight were at the fifth percentile (152 cm and 37 kg, respectively). He had bilateral ptosis more prominent on the left eye. His left pupil was mildly dilated and responded poorly to light; elevation of both

* From the Infectious Diseases Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara.
** Research Assistant in Pediatrics, Hacettepe University Faculty of Medicine.
*** Associate Professor of Pediatrics, Hacettepe University Faculty of Medicine.
**** Professor of Pediatrics, Hacettepe University Faculty of Medicine.

eyes and convergence were also limited. The plantar response was extensor on the right side. His vital signs were stable and the physical examination was otherwise unremarkable.

Complete blood cell count, urinalysis and blood chemistry were all normal as were the chest roentgenograms. Cerebrospinal fluid (CSF) examination revealed a total of 90 cells/mm^3 with a lymphocyte predominance. CSF protein was 32 mg/dl, and cultures including for tuberculosis and fungi were all negative. Tuberculin skin test was negative. Polymerase chain reaction (PCR) in the CSF was positive for tuberculosis. A cranial computed tomography revealed communicating hydrocephalus, and cranial magnetic resonance imaging was performed.

After gadolinium injection, T1-weighted MR images showed multiple tuberculomas enhancing in the mesencephalon, suprasellar cistern and bilateral hippocampi (Figs. 1, 2).

The patient's signs and symptoms gradually subsided after the start of antituberculous therapy with isoniazid, pyrazinamide and ethambutol, and responded better to a ventriculoperitoneal shunt. He was discharged from the hospital in good clinical condition without any gaze palsy.

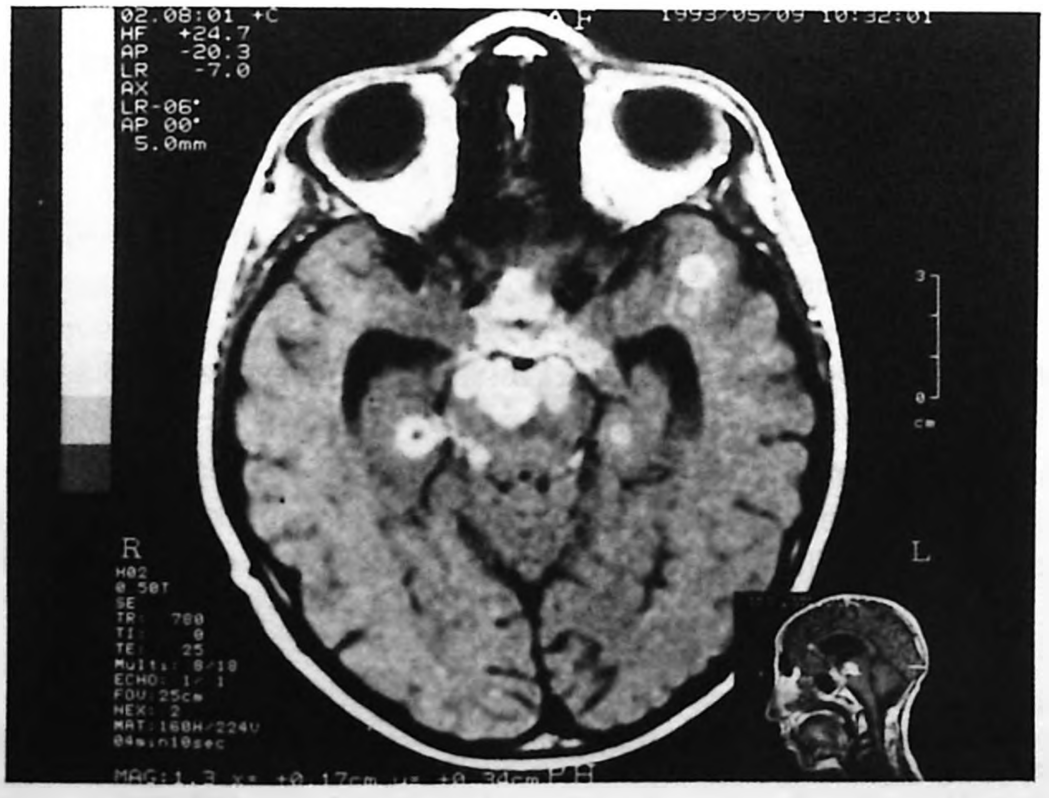

Fig. 1: Axial T1-weighted MR image after gadolinium injection showed multiple tuberculomas enhancing in the mesencephalon, suprasellar cistern and bilateral hippocampi, and a nodular enhancing lesion in the corpus callosum was noted on the sagittal "survey" view.

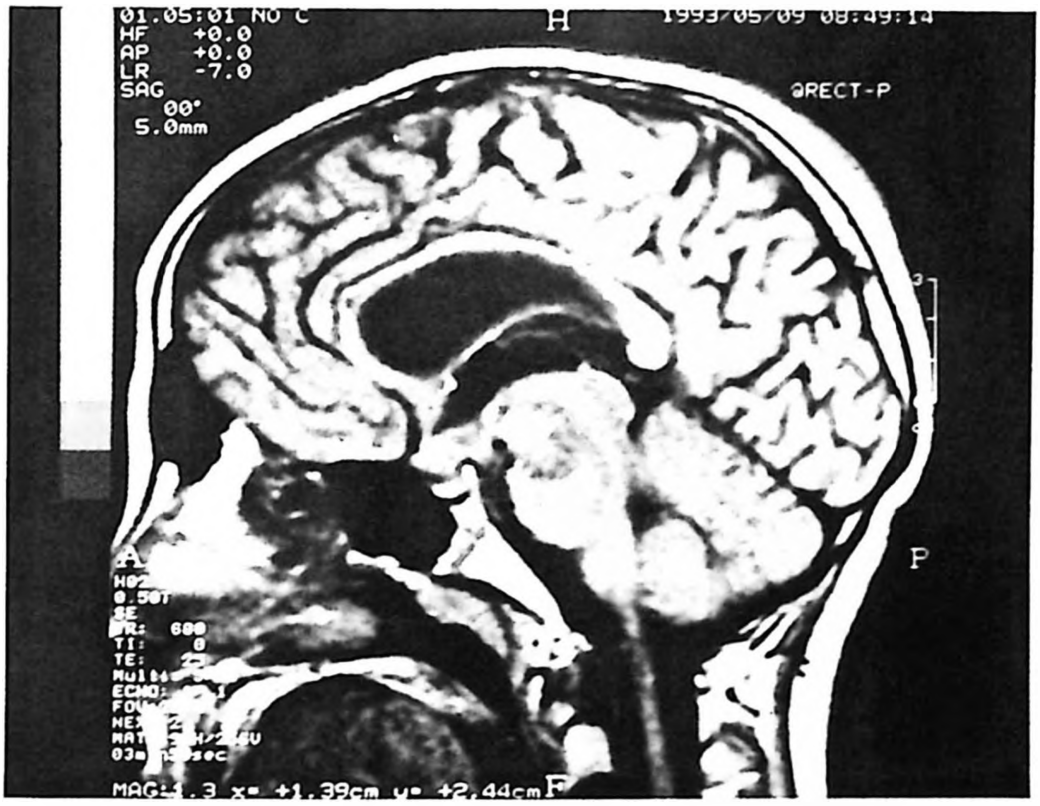

Fig. 2: Sagittal T1-weighted image showing tuberculomas in the mesencephalon and suprasellar cistern. There was a minute hyperintense lesion in the corpus callosum.

Discussion

Tuberculomas represent the most common parenchymal form of the CNS tuberculoses[1]. Only 15 to 40 percent of tuberculomas are multiple, and 60 percent are infratentorial, more commonly in children[1]. The frontal and parietal lobes are most commonly involved[2]. A prolonged febrile illness progressing to vomiting and lethargy is the usual course of intracranial tuberculoma. Signs and symptoms of increased intracranial pressure, such as headache, seizures and gaze palsies are common, as in our patient.

Intracranial tuberculomas are space-occupying masses of granulomatous tissue that result from hematogenous spread from a distant focus of tuberculous infection. They originate as a conglomerate of small tubercles that join to form a mature tuberculoma composed of a necrotic caseous center surrounded by a capsule containing collagenous tissue, epithelioid cells, Langhans giant cells and lymphocytes[3]. Tuberculomas are mostly diagnosed during antituberculous treatment and are uncommon in patients with active tuberculosis.

New neurological signs such as ocular motility disorders and hydrocephalus during antituberculous treatment are not unusual with tuberculomas, and these

signs and symptoms seen 10 days to five months after the start of treatment have led to the recognition of most tuberculomas[4]. Paradoxical expansion of cerebral tuberculomas and the appearance of symptoms during antituberculous treatment are explained by a complex host-organism interaction. Chemotherapy of any tuberculous locus causes destruction of acid fast bacilli and liberation of tuberculoprotein, probably invoking an inflammatory response with resulting edema and swelling of the focus. The mechanism may be similar to cervical lymph node enlargement due to trapping of antigen-reactive lymphocytes[4].

In all reports of MR with gadolinium-DTPA enhancement, intracranial tuberculomas have showed homogenous enhancement. Without gadolinium-DTPA enhancement, the MR images are generally insensitive to detection of active meningeal inflammation and granulomas. MRI is the technique of choice for the detection of subtle brain involvement in central nervous system tuberculosis and tuberculomas[6]. The signal intensity of granulomas on MRI is usually isointense to the gray matter on both T1- and T2-weighted images. On gadolinium-DTPA-enhanced T1-weighted images, granulomas often appear as conglomerated ring-enhancing nodules, as in our case[6]. Gadolinium-DTPA-enhanced MR imaging appears to be superior to computerized tomography in the evaluation of active or subtle intracranial tuberculosis[1,6].

The diagnosis of intracranial tuberculoma should rest on proper integration of data from clinical manifestations, cerebrospinal fluid analysis and neuroimaging studies. Objective evidence of systemic tuberculosis or exposure to disease may be absent in up to 70 percent of cases[3]. Tuberculous abscesses, gliomas, metastases, meningiomas, cysticercosis, coccidiomycosis and tuberous sclerosis should all be considered in the differential diagnosis[7]. There was also no evidence of systemic tuberculosis in our patient. Our patient did not have all the diagnostic criteria, such as positive smears for acid fast bacilli, positive cultures or a positive tuberculin test[8]. There was also no close family member with active tuberculosis. His CSF findings with a lymphocyte predominance and low glucose were compatible with tuberculous meningitis. Polymerase chain reaction for mycobacterium tuberculosis was positive in the CSF.

PCR is found to be a rapid diagnostic method for the diagnosis of CNS tuberculosis, especially tuberculous meningitis[9]. PCR is more sensitive than the conventional bacteriological methods, which are inadequate for the early and exact diagnosis of CNS tuberculosis. There are few organisms in the CSF for demonstration by direct smear; cultural identification takes six to eight weeks and unfortunately culture yields are mostly poor, as in our case. Under these circumstances, the use of PCR, especially in developing countries, is feasible[9].

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DIAGNOSTIC VALUE OF RENAL ARTERIOGRAPHY IN POLYARTERITIS NODOSA*

*Neslihan Tekin MD***, *Nurdan Kural MD****, *Tamer Kaya MD*****

SUMMARY: Tekin N, Kural N, Kaya T. (Departments of Pediatrics and Radiology, Osmangazi University Faculty of Medicine, Eskişehir, Turkey). Diagnostic value of renal arteriography in polyarteritis nodosa. Turk J Pediatr 1986; 38: 101-105.

Polyarteritis Nodosa (PAN) is a rare disease in childhood. No single pattern of clinical presentation characterizes this disease, but abdominal pain, central or peripheral nervous system disease, arthritis, myalgia and skin lesions occur at some time during the course of the illness. In this case a 16-year-old boy who presented with abdominal pain, elevated sedimentation rate associated with hypertension, and a high level of renin, all of which were detected during his hospitalization, suggested the diagnosis of PAN, and renal angiography was performed. Characteristic renal aneurysms were visualized and the diagnosis was confirmed. *Key words: renal arteriography, renal aneurysms, polyarteritis nodosa, hypertension.*

Polyarteritis nodosa (PAN) is a well-known form of necrotizing angiitis which is characterized by focal necrosis of the walls of small- and medium-sized arteries[1-3]. The angiitis of polyarteritis affects various organs singly or in combination. Kidney, skin, joints, heart, peripheral nerves and the gastrointestinal tract are the most common sites of involvement[4, 5]. Lung, skeletal muscle and central nervous system involvement can occur at any time during the course of the disease.

The diagnosis of PAN is based on clinical evidence of multi-organ involvement corroborated by demonstration of vasculitis by either histopathologic changes on biopsies of skin, muscle or kidney, electrocardiography, electromyography or arteriography[6]. It is a rare disease of childhood and in most cases diagnosis is not confirmed early in the course of the disease because PAN closely mimics many diseases, especially the other collagen tissue disorders. In some cases biopsy is not diagnostic.

In this case the diagnosis of PAN was established by demonstrating aneurysms in the renal arteriography of a 16-year-old patient. We report this case to draw attention to the diagnostic value of renal arteriography in PAN-suspected cases, especially when, histopathological evaluation is not helpful in identifying the diagnosis.

* From the Departments of Pediatrics and Radiology, Osmangazi University Faculty of Medicine, Eskişehir.

** Assistant Professor of Pediatrics, Osmangazi University Faculty of Medicine.

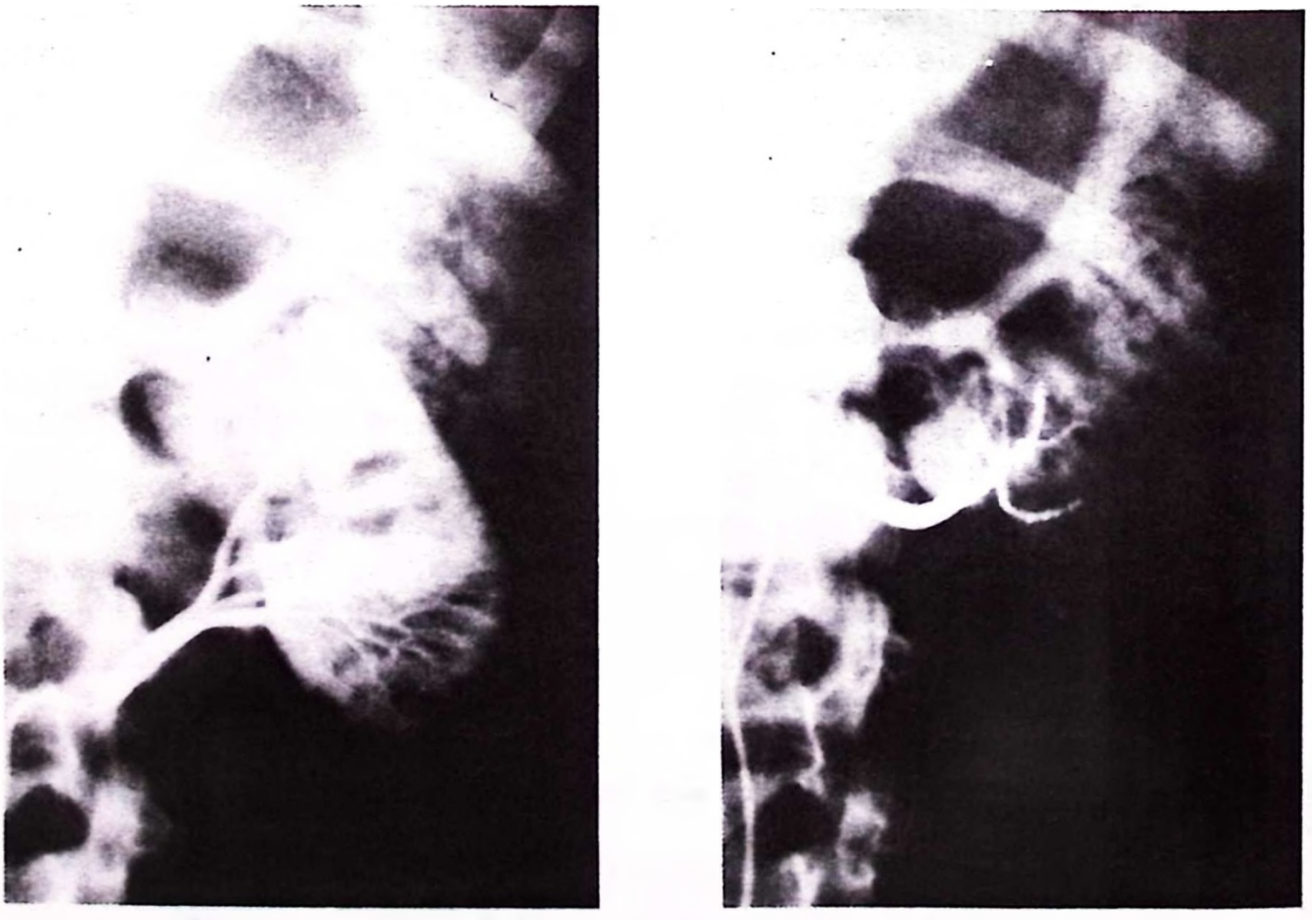
*** Professor of Pediatrics, Osmangazi University Faculty of Medicine.

**** Associate Professor of Radiology, Osmangazi University Faculty of Medicine.

Case Report

A 16-year-old boy presented with abdominal pain. He had been suffering continuous pain around his umbilicus which extended towards both costolumbar regions for 14 days.

Vital signs: blood pressure 120/80 mmHg, heart rate 64/min, temperature 36.7 °C. Tenderness was present during palpation of both of the costolumbar regions. His physical examination was otherwise unremarkable. The hemogram revealed Hb 13.2 g/dl, platelets 355.000/mm^3, total white cell count 12.100/mm^3 with 75% neutrophils and 25% lymphocytes. Erythrocyte sedimentation rate 65 mm/h, Fibrinogen 575 mg/dl. Urinalysis repeated five times was normal. BUN 20 mg/dl, Cr 1 mg/dl, blood glucose 101 mg/dl, Ca 10 mg/dl, Na 141 mEq/L, K 4.8 mEq/L, SGOT 30 U/L (7-39), SGPT 25 U/L (2-54), Alkaline phosphatase 65 U/L (41-133), total protein 7.5 g/dl, albumin 3.9 g/dl, amylase 120 mg/dl (50-180), renin 7 ng/ml (1.5-5.7), aldosterone 52 ng/dl (12-125), ASO 833 Todd U, CRP 24 mg/dl, HBsAg (-), IgG 2400 mg/dl (800-1700), IgA 266 mg/dl (85-490), IgM 99.3 (50-370) mg/dl, C3 89.8 mg/dl (50-90), C4 46.1 mg/dl (10-40), ANA (-), anti DNA 4.26 IU/ml (0-6). No pathogenic microorganism was detected in cultures taken from the throat, urine



Figs: 1 and 2: Renal arteriography showing the characteristic aneurysms.

or stool. Chest roentgenogram, ultrasonography and computed tomography of the abdomen, biopsy of the skin, subcutaneous tissue and muscle were all normal.

During the course of hospitalization hypertension was detected up to 160/110 mmHg and persisted at high levels. When a high level of renin was found, renal artery angiography was performed to evaluate the case. Renal aneurysms characteristic of PAN were visualized (Figs. 1 and 2). Steroid therapy was administered and the patient was followed up.

Discussion

The diagnosis of polyarteritis nodosa is based on clinical evidence of multisystemic involvement, biopsies of the kidney, muscle or skin and selective arteriography of the kidney, hepatic or mesenteric arteries[4]. As it is known that PAN in children is such a serious and often rapidly fatal disease, early recognition and treatment are important. Diagnosis with only clinical features may not be correct. If clinical or laboratory evidence suggests the diagnosis of PAN, biopsy or arteriography of selected tissues should be performed.

Özen et al.[7] established two major and ten minor findings of the disease as diagnostic criteria of PAN in children. The presence of five of these 12 criteria, including at least one major criterion, has been used to indicate the diagnosis of PAN, but in most of the series the diagnosis needed to be confirmed by either biopsy or arteriography.

Abdominal pain, the most common gastrointestinal symptom in PAN, was our patient's only complaint. In Pediatric PAN series, it has been reported that abdominal pain was a complaint in 20 of 25 in one group and 10 of 11 in the other[5, 8]. When the other series are combined, abdominal pain was present in 67 percent of patients[5].

Renal involvement in PAN can conveniently be divided into two distinct types: one affecting medium-sized extraglomerular vessels (classical macroscopic PAN) and the other characterized by microscopic arteriolar/capillary involvement and glomerulonephritis[9]. Aneurysmal dilatation is classically confined to medium-sized vessels and is seen in angiography. Although hypertension occurs more frequently among those individuals whose arterial lesions involve medium-size vessels, it may also develop as a result of glomerular involvement[9]. In this case because the urinary findings and renal function studies were normal, we believed that the hypertension originated from the involvement of medium-sized extraglomerular vessels. That was proved by the elevated renin level and formation of renal artery aneurysms. The incidence of hypertension varies among the series. All 11 children with PAN reported by Blau et al.[8] had hypertension. In the report of Özen et al.[7], hypertension developed in 20 out of 31 cases. In a study of 36 PAN cases, hypertension was the second most common clinical with an incidence of 83 percent[5].

Elevated ESR, CRP and mild leukocytosis were present in our case, which may be accepted as nonspecific laboratory findings of PAN. However, the features described here are not enough to confirm the diagnosis. The demonstration of perinuclear-anti-neutrophil cytoplasmic antibodies (p-ANCA), which is usually associated with PAN and other vasculitides, would be more helpful in making a specific diagnosis[9].

Typical involvement of medium-sized muscular arteries and small arteries could not be demonstrated in our patient's skin biopsy. Biopsies of skin or muscle are the easiest to obtain but are frequently normal, especially if the specimen is taken from an uninvolved site. Because of normal urinary findings and renal functions we did not consider doing a kidney biopsy. Renal arteriography was performed, and characteristic renal aneurysms were visualized. The first case with PAN diagnosed by renal angiography in the pediatric age-group was reported in 1972 by McLain et al.[10] but when compared with our case he had several other manifestations of the disease, even myocardial infarction. Angiography has a 90, 94 percent sensitivity in adult patients with PAN[11]. The abnormalities include both arterial aneurysms and occlusions. The mechanism of formation of aneurysms is the weakened wall which tends to bulge because of fibrinoid necrosis, and inflammation with polymorphonuclear leukocytes, eosinophils, and round cells[12].

In this case we draw attention to the diagnostic value of arteriography when the clinical features are not clear and biopsy does not show the characteristic histopathological changes.

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TRANSCATHETER EMBOLIZATION OF A PULMONARY COLLATERAL VESSEL IN A CHILD WITH TRICUSPID ATRESIA*

Case Report

*Sevim Karaaslan MD***, *Alpay Çeliker MD***, *Nazlıhan Günal MD****

SUMMARY: Karaaslan S, Çeliker A, Günal N. (Cardiology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Transcatheter embolization of an aortopulmonary collateral vessel in a child with tricuspid atresia: case report. Turk J Pediatr 1986; 38: 107-111.

When a significant systemic-pulmonary arterial collateral connection occurs in children with cyanotic congenital heart disease, they may present surgical difficulties making operative management undesirable. Transcatheter vessel occlusion can be a life-saving procedure or an important adjunct in reducing blood loss during surgery.

This report describes the selective obliteration of a large systemic pulmonary arterial collateral vessel in a child with tricuspid atresia before Fontan operation. A transcatheter wire coil embolus technique was used, and no complications or errors in placement of the coils occurred. *Key words: tricuspid atresia, aortopulmonary collateral vessel, coil embolization.*

Transcatheter vascular occlusion utilizing the stainless steel coil has found applications in the control of hemorrhage, the management of neoplasm and complex aneurysms of the vertebrobasilar circulation, the closure of the small patent ductus arteriosus, and the nonsurgical treatment of arteriovenous fistulas and aortopulmonary collateral vessels in patients with congenital heart disease[1-9].

This report describes a steel coil embolization of a collateral vessel in a child with tricuspid atresia.

Case Report

A five-month-old girl was referred to the Pediatric Cardiology Unit of Hacettepe University in June 1989 for cyanosis which had first been noted when she was three months old. She was cyanotic, and auscultation of the heart revealed a grade III/VI ejection systolic murmur on the left sternal border. The electrocardiogram revealed tall P waves, left axis deviation and left ventricular hypertrophy. The chest radiogram showed oligemic lung fields and cardiomegaly. The echocardiographic examination revealed tricuspid atresia.

* From the Cardiology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara.

** Associate Professor of Pediatrics and Pediatric Cardiologist, Hacettepe University Faculty of Medicine.

*** Pediatrician and Fellow in Cardiology, Hacettepe University Faculty of Medicine.

In view of the patient's worsening condition and increasing cyanosis, cardiac catheterization was performed at age two years. Normally related great arteries, a restrictive ventricular septal defect and pulmonary stenosis were demonstrated, and a left Blalock-Taussig shunt was contemplated.

When the patient was five years old, cardiac catheterization was performed again in order to measure the pulmonary artery pressure before Fontan operation. The left Blalock-Taussig shunt was present, and the pressure was 100/4 mm Hg in the left ventricle and 16/4 mm Hg (mean: 12 mm Hg) in the pulmonary artery. The antero-posterior and lateral angiograms of the descending aorta demonstrated an aortopulmonary collateral vessel that could not be achieved via median sternotomy, so the day before the operation this aortopulmonary collateral vessel was occluded with coil (Fig. 1).

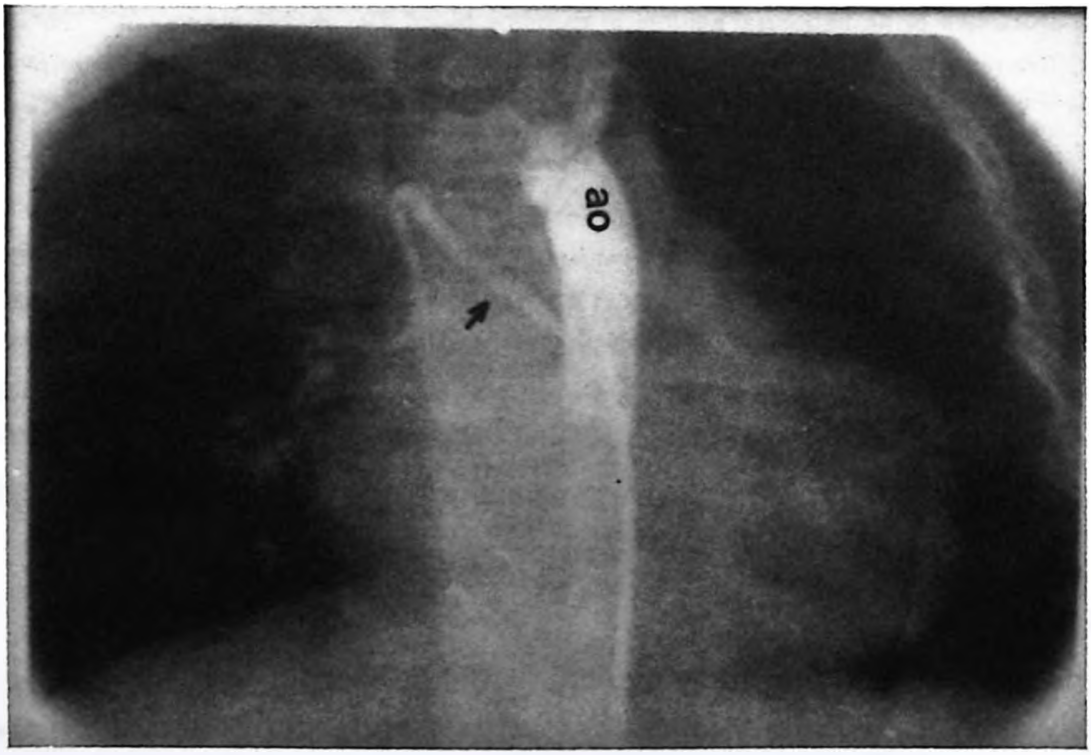

Fig. 1: Aortogram before embolization. Arrow shows collateral vessel. ao = descending aorta.

The patient received antibiotic prophylaxis with cefazolin before and for 24 hours after coil embolization. Routine precatheterization sedation with pethidine HCl, chlorphenoxamine and chlorpromazine combination was used, followed by diazepam during the procedure. Intravenous heparin was given when vascular access had been obtained.

The collateral vessel was precisely localized by hand injection of contrast material into the collateral. Embolization was performed by transarterial approach, and a number six French end-hole catheter was sufficient for coil placement. A 0.035-

inch guide wire was used to push the coil from the catheter into the vessel. Three coils, two measuring 4 cm x 3 mm and one 3 cm x 5 mm. (occluding spring coil, Cook Inc.), were extruded through the catheter.

Fifteen minutes after the last spring coil placement, a descending aortic angiogram revealed no blood flow into the collateral vessel (Fig. 2). The procedure was terminated with no complications, and the patient underwent a Fontan operation in the Cardiac and Thoracic Surgery Department of Hacettepe University.

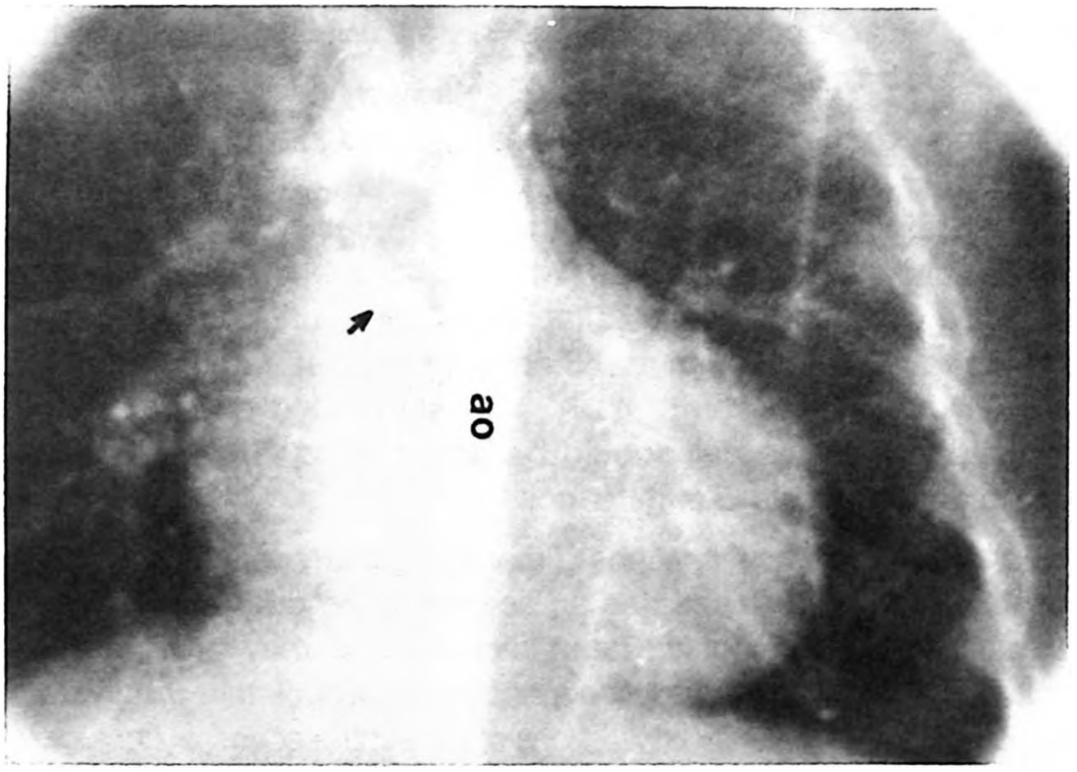

Fig. 2: Aortogram after embolization demonstrates occluded collateral vessel (arrow: spring coils) ao = descending aorta.

Discussion

The association of large systemic-pulmonary collateral blood vessels in cyanotic congenital heart disease is well known. If major collateral vessels are left unattended, maintenance of adequate perfusion pressure is difficult and achieving optimal surgical exposure without circulatory arrest is at times impossible because of voluminous cardiac return of blood which leads to flooding of the operative field.

Objective assessment of the hemodynamic significance of collateral vessels in patients who have already undergone corrective surgery is difficult[7]. According to Wernovsky et al.[10], the presence of cardiomegaly, continuous murmur, elevated left ventricular end-diastolic pressure, pulmonary artery hypertension or prompt visualization of pulmonary veins and the left atrium after injection of contrast

medium into the aorta or left ventricle may indicate significant flow into the pulmonary vascular bed; in such cases, embolization of these vessels is indicated. Thus careful preoperative angiographic assessment of the size and location of the collateral vessels is essential to determine which of these vessels might best be approached surgically and which might best be occluded by the catheter technique.

In our case, angiographic examination of the descending aorta demonstrated significant flow into the pulmonary vascular bed via a collateral vessel; thus this collateral vessel was chosen to occlude with coil before Fontan operation because of its anatomic localization.

The length and shape of the coil when embolized depend on a number of factors, including the ratio of coil to vessel diameter, the distensibility of the vessel and the diameter of the wire in the coil. In our case a 4 cm long, 3 mm diameter "occluding spring embolus" was implanted into the collateral vessel but it remained patent 10 minutes after the placement, and an additional two coils were placed (4 cm x 3 mm and 3 cm x 5 mm) depending on the anatomy of the vessel and the position of the previously placed coil or coils. Perry et al.[7] demonstrated that the coil should be about 10 to 40 percent larger than the vessel diameter, as in our third coil.

Coil embolization is an attractive means of managing many difficult clinical problems. The procedure may be performed as an adjunct to the operative management of children with complex congenital heart disease and may provide a practical, cost-effective alternative to the operative managemenat of certain congenital thoracic vascular anomalies[8]. However, complications of transcatheter vessel occlusion include reflux and occlusion of nontarget vessels, tissue ischemia with pain, tissue necrosis, altered organ function, fever, sepsis and miscellaneous mechanical complications[11]. Nonetheless, considerable clinical experience has demonstrated that coil embolization is a safe and effective procedure, as in our case[7,8].

In summary, this report described a succesful coil embolization of a collateral vessel in a child with tricuspid atresia before Fontan operation, and this was the third application of coil into a collateral vessel at our institute.

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CONGENITAL CHYLOTHORAX*

*Hasan Özkan MD***, Naim Ay MD****, Dinç Özaksoy MD*****
*Derya Erçal MD***, Yakup Erata MD******, Hatice Durak MD*******
*Özcan Evyapan MD****, Suphi Toprak MD*******

SUMMARY: Özkan H, Ay N, Özaksoy D, Erçal D, Erata Y, Durak H, Evyapan Ö, Toprak S. (Department of Pediatrics, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey). Congenital chylothorax. Turk J Pediatr 1986; 38: 113-117.

Congenital chylothorax is a rare condition in which chyle accumulates in the pleural space because of an intrauterine obstruction or anomalies of the thoracic duct. This paper presents a case of congenital chylothorax diagnosed antepartum echographically. The patient's history revealed a previous sibling with a similar diagnosis. The baby developed respiratory distress after delivery and the diagnosis was established by thoracentesis. Computed tomography of the chest and nuclear lymphangiography were obtained to evaluate the origin of the pleural effusion, but a congenital fistula or other pathology of the thoracic duct could not be demonstrated. Management of the baby consisted of ventilatory support in the delivery room, repeated thoracentesis and thoracostomy tube drainage, total parenteral nutrition and formula containing medium-chain triglycerides. The infant was discharged six weeks after birth in good condition.
Key word: congenital chylothorax.

Chylothorax is a rare cause of pleural effusion, although it is the most common cause of pleural effusion in the neonatal period[1]. Chylothorax most commonly occurs following thoracic surgery along with mediastinal masses and rarely in the neonatal period, idiopathically[2]. Chylothorax results from the escape of chyle from multiple fistulas of the malformed thoracic duct, but the anatomical defect can be demonstrated in few cases[1]. Though chylothorax is seen more commonly on the right side due to the duct's greater length on this side, it can also occur bilaterally or on the left side[3,4]. It occurs twice as often in males, and the incidence has been reported as 1/10.000-15.000[5,6]. In this report, a male infant with congenital chylothorax who had ultrasonographically established "isolated right pleural effusion" in the 36th week of gestation and a history of a sibling death with similar complaints, is presented.

* From the Department of Pediatrics, Dokuz Eylül University Faculty of Medicine, İzmir.
** Associate Professor of Pediatrics, Dokuz Eylül University Faculty of Medicine.
*** Research Assistant in Pediatrics, Dokuz Eylül University Faculty of Medicine.
**** Associate Professor of Radiology, Dokuz Eylül University Faculty of Medicine.
***** Obstetrician and Gynecologist, Dokuz Eylül University Faculty of Medicine.
****** Associate Professor of Nuclear Medicine, Dokuz Eylül University Faculty of Medicine.

Case Report

A 27-year-old woman, para 1, was referred to the perinatal unit of Dokuz Eylül University School of Medicine for evaluation of a right pleural effusion in the fetus, which was noted during a routine ultrasound examination at 36 weeks. The first baby of the family had died at six days of life due to respiratory distress with an autopsy finding consistent with the diagnosis of left lung hypoplasia. This clinical picture was believed to be most consistent with left congenital chylothorax. The infant was delivered by cesarean section at 37 weeks.

The infant weighed 3000 g and had Apgar scores of four and six at one and five minutes, respectively. The baby was resuscitated in the delivery room, and mechanical ventilation was begun. Physical findings revealed a depressed baby with respiratory difficulty and absent breath sounds in the right hemithorax. Right-sided thoracentesis was performed in the delivery room, producing approximately 170 ml of straw-colored fluid. The fluid contained 10.000 leukocytes/ml with a differential count of 96% lymphocytes and 4% granulocytes. The protein and glucose contents were 3.6 g/dl and 137 mg/dl, respectively. The density was 1015, and the pH of the fluid was 8. Triglyceride and cholesterol contents were 22 mg/dl and 24 mg/dl, respectively. Cultures of fluid were negative. Other laboratory investigations revealed normal urinalysis, complete blood count, blood urea nitrogen, creatinine, liver function tests, electrolytes, total protein (5.9 g/dl), albumin (3.2 g/dl), triglyceride (100 mg/dl), cholesterol, glucose (138 mg/dl), amylase and lactic dehydrogenase levels. Blood gases demonstrated respiratory acidosis. Serologic tests for toxoplasma, rubella and cytomegalovirus were negative. X-ray, ultrasonography and computerized tomography of the chest demonstrated a right pleural effusion with normal parenchyme and mediastinum (Figs. 1, 2, 3). Nuclear lymphangiography was

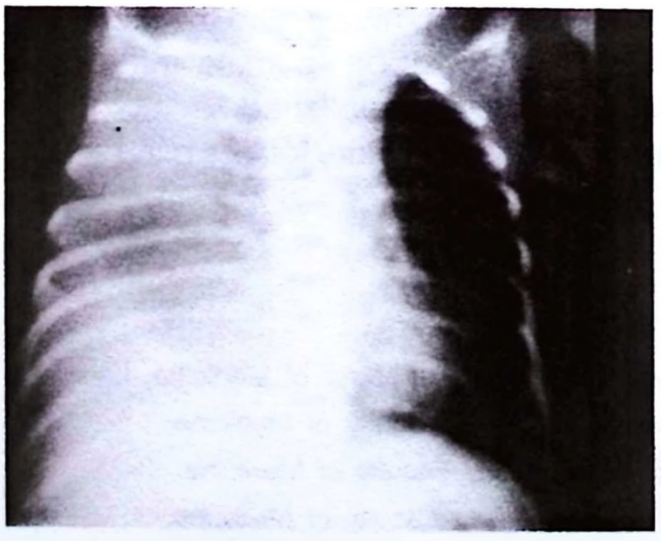

Fig. 1: Chest x-ray of the baby before thoracentesis.

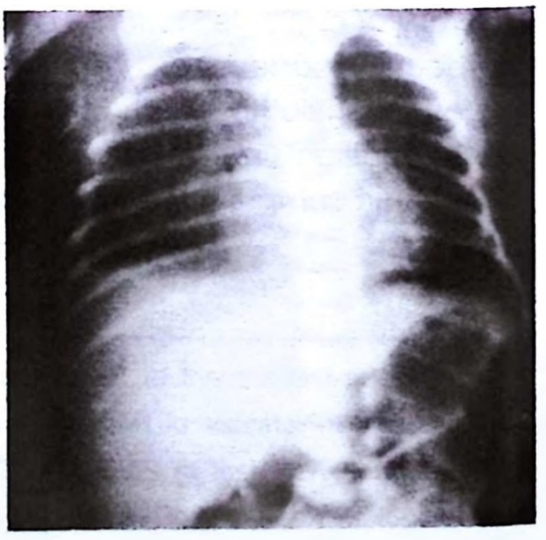

Fig. 2: x-ray of the baby after thoracentesis.

normal (Fig. 4). Repeated thoracentesis was performed because of reaccumulation. On the fifth day of life, the baby was extubated and oral feedings were begun. After the infant began feeding, the pleural fluid had a milky appearence with a high triglyceride level (140 mg/dl).

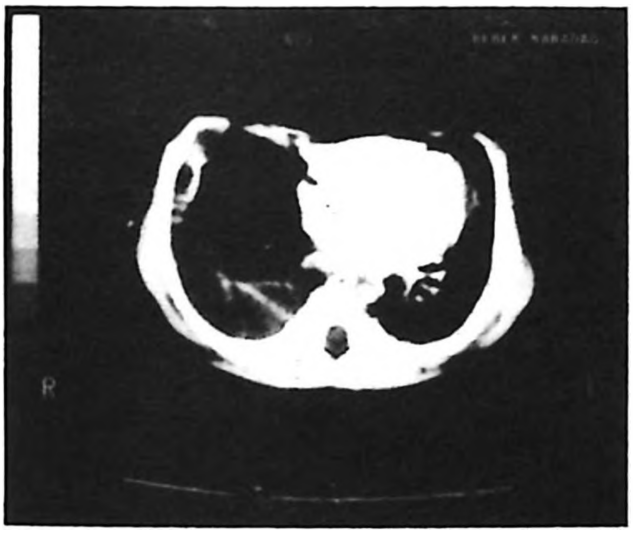

Fig. 3: Thoracal CT before thoracentesis.

Fig. 4: Scintigraphic lymphangiography.

Recovery occurred after treatment with repeated thoracentesis for four weeks and thoracostomy tube drainage for two weeks. During this period, the baby received total parenteral nutrition and then a formula containing medium chain triglyceride. The infant was discharged six weeks after birth in good condition, receiving breast milk.

Discussion

Chylothorax results from the leakage of chyle from the thoracic duct into the thoracic cavity. The fluid is milky, odorless and alkaline with a density of 1012, is biochemically composed of protein, glucose, urea and electrolyte contents identical with plasma, and is rich in triglycerides and lymphocytes[7-9]. The definitive diagnosis is established when the thoracentesis demonstrates a fluid with a chylomicron concentration of 110 mg/dl. However, the pleural fluid usually demonstrates this property after enteral feeding is started[7]. Though congenital chylothorax results from congenital anomalies and obstructions of the thoracic duct, the etiology usually remains unclear. It is also associated with congenital goiter[4], lung tumors[10], congenital lymphangiectasis[3], pulmonary sequestration[11], congenital cytomegalovirus[6] and adenoviral infections[12], right diaphragmatic hernia and group B streptococcal infections[13]. In our case, we could not identify any specific etiology. Hagay et al.[14] have reported that congenital chylothorax

might be associated with Down, Turner or Noonan Syndromes or congenital heart disease. Our case had atrial and ventricular septal defects. The most prominent finding in these patients is respiratory distress in the postnatal period due to fluid collection.

In cases of chylothorax there is increased dullness on precussion and the breath sounds are suppressed on the affected side[15]. The ultrasonograph can detect fluid collection in the gestational period which may be associated with polyhydramnios[15, 16]. Treatment is mainly conservative. Most of the cases without respiratory distress recover spontaneously. Repeated aspirations may be needed in cases with respiratory distress. Chest tube drainage may be performed in persistent cases, and if the region of leakage cannot be detected, pleurodesis may be indicated[17, 18]. Fluid, electrolyte, lipid and lymphocyte loss, pneumothorax and infection may be associated with repeated thoracenteses. The patient should be fed with total parenteral nutrition, while medium-chain triglycerides, which pass directly into the venous circulation, should be started for enteral feeding[19]. In our patient, ventilatory support was done for respiratory distress and repeated thoracenteses and chest tube drainage were carried out. He was fed with TPN, and formula containing medium chain triglycerides was started for enteral feeding.

Management after intrauterine diagnosis is not certain, as a limited number of studies and cases have been reported. Repeated thoracenteses or pleuro-amniotic shunt procedures are suggested in intrauterine-diagnosed cases, if an increase in fluid collection is observed[14]. The pleuro-amniotic shunt procedure is reported to increase survival[15]. Perinatal mortality rates range between 15 and 30 percent. Prematurity, accompanying pulmonary hypoplasia and development of non-immune hydrops increase mortality.

Mortality increases to 55 percent in cases with established pleural effusion earlier than the 32nd week of gestation[14]. In our case, absence of pulmonary hypoplasia development suggests that chylothorax had developed in the late gestational period, leading to a good prognosis. The clinical improvement of our case suggests the importance of antenatal diagnosis, early intervention and appropriate follow-up.

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HIGH – DOSE INTRAVENOUS IMMUNE GLOBULIN IN THE MANAGEMENT OF SEVERE GUILLAIN – BARRÉ SYNDROME*

*Esra Baskın MD***, *Sadi Türkay MD***, *Dilara İçağasıoğlu MD***
*Fatoş Tanzer MD****; *Ömer Cevit MD*****

SUMMARY: Baskın E, Türkay S, İçağasıoğlu D, Tanzer F, Cevit Ö. (Department of Pediatrics, Cumhuriyet University Faculty of Medicine, Sivas, Turkey). High-dose intravenous immune globulin in the management of severe Guillain-Barré syndrome. Turk J Pediatr 1986; 38: 119-123.

Guillain-Barré Syndrome (GBS) is the most common cause of acute generalized paralysis. Although the cause and pathogenesis of GBS remain unknown, there is increasing evidence to suggest that this syndrome has an immunological basis. Two children suffering from GBS were treated with high-dose intravenous immune globulin (IVIG) (1 g/kg/day over two consecutive days). Both children showed marked clinical improvement within 48 hours of the onset of treatment. It is suggested, on the basis of recent case reports, that immunoglobulins may have an important role in the treatment of Guillain-Barré Syndrome.
Key words: intravenous immunoglobulin, Guillain-Barré syndrome.

Guillain-Barré Syndrome (GBS) is the most common cause of acute generalized paralysis, with an annual incidence of 0.75 to 2 cases per 100.000 population[1,2]. It is characterized by demyelination of peripheral nerves and causes a flaccid paralysis, autonomic dysfunction and minor sensory symptoms. The mortality rate is approximately five percent. In addition, 10 to 30 percent of patients require artificial ventilation, and three to 10 percent experience relapses. Although functional recovery is the rule, 20 percent of patients have residual disability[3-5]. The likelihood of permanent disability increases with the severity and duration of the disease, and patients may require prolonged hospital care. There is therefore an urgent need for a form of treatment that would decrease the severity of the acute phase of the disease and shorten the recovery period.

There is increasing evidence to suggest that this syndrome has an immunological basis. Recently it has been shown that high-dose intravenous immune globulin (IVIG) may be of benefit in GBS[6-8]. Here we present two cases of GBS who were given high-dose IVIG. Although the usual dose of IVIG is 400 mg/kg/day for five days, we administered 1 g/kg/day over two days as reported in Shahar et al.'s study[7].

* From the Department of Pediatrics, Cumhuriyet University Faculty of Medicine, Sivas.
** Assistant Professor of Pediatrics, Cumhuriyet University Faculty of Medicine.
*** Professor of Pediatrics, Cumhuriyet University Faculty of Medicine.
**** Research Assistant in Pediatrics, Cumhuriyet University Faculty of Medicine.

Case Reports

Case 1

An eight-year-old girl who was previously healthy was admitted with a seven-day history of generalized arthralgia and myalgia mainly in the lower limbs following an upper respiratory tract infection. She was unable to stand and could not raise her legs from the bed due to pain. Two days later the weakness in the lower limbs become more marked, and progressed to involve all muscle groups. There was evidence of decreased deep tendon reflexes and cranial nerve involvement with marked facial weakness, decreased pharyngeal reflexes, nasal voice and difficulties in swallowing and breathing. Her forced vital capacity (FVC) was 0.70, which was 32 percent of the predicted value. Arterial blood gases were as follows: pH 7.42, arterial carbon dioxide tension 40 and arterial oxygen tension 60. The cerebrospinal fluid protein content was elevated to 103 mg/dl with no cells. Initial investigations revealed normal hematological and biochemical indices. Results of bacterial and viral studies of blood and cerebrospinal fluid were negative.

A diagnosis of Guillain-Barré syndrome was made according to the criteria of Ausbury and Cornblath[9]. IVIG (Sandoglobulin, Sandoz Pharmaceuticals) was given intravenously at a dose of 1 g/kg/day over two consecutive days. During the infusions the patient was monitored for side effects, including alterations in heart rate, respiratory rate, blood pressure and temperature. There was no treatment added after IVIG. Clinical improvement began 24 hours after the beginning of IVIG therapy with improvement in breathing difficulty, and at 48 hours improvement in facial diplegia and swallowing difficulty were seen. At the end of the fifth day of therapy, the patient was sitting and walking with support. FVC increased to 70 percent of the predicted value on the eighth day.

She was sent home on the 15^{th} day of hospitalization. On her outpatient follow-up visit two months later, complete clinical recovery from illness and no abnormality of the musculoskeletal system were seen.

Case 2

A previously well 12-year-old boy was admitted with a four-day history of progressive weakness and pain in his feet and legs following mild gastroenteritis. On examination he had flaccid paralysis and hyporeflexia affecting all four limbs symmetrically with reduced strength. His proximal muscle groups were affected most severely. Decreased pharyngeal reflexes, diplopia and difficulty in breathing were seen. Vital capacity declined to 20 percent of predicted value, and arterial blood gases were as follows: pH: 7.43, $PaCO_2$ 35, PaO_2 76. The cerebrospinal fluid was cellular with the protein concentration elevated to 182 mg/dl. The hematological and biochemical results were within normal limits. Bacterial and

viral studies of blood and cerebrospinal fluid were done, and only the cytomegalovirus serologic test was found to be positive.

The patient's clinical presentation and laboratory parameters led to the diagnosis of Guillain-Barré syndrome[9]. He was intubated and ventilated. Treatment with IVIG was given at a dose of 1 g/kg/day over two consecutive days. No side effects occurred during IVIG therapy. Fourty-eight hours after treatment, he was extubated and was able to sit with support. Within eight days of the start of IVIG infusion, he was able to walk more than five meters with assistance. Improvement continued gradually, and 10 days after the completion of therapy FVC returned to normal.

The patient was sent home on the 30th day of hospitalization with complete clinical recovery. No recurrence of symptoms was observed during the subsequent one-year follow-up period.

Discussion

The acute polyneuropathy of GBS often affects peripheral nerves. Typically a nonspecific prodromal illness is followed one to 28 days later by the onset of weakness which progresses over the next seven to 14 days, generally reaching a peak by day 10. A plateau period lasting 5 to 46 days (mean 10.5 days) precedes the onset of recovery, which is complete by 2.5 to 15 months[4]. Difficulty in swallowing and impaired respiration are the most serious symptoms. Mechanical ventilation may be needed for as long as eight weeks, with subsequent possible complications such as pneumonia and pneumothorax[7].

Although the cause and pathogenesis of GBS remain unknown, it has been proposed that anti-peripheral nerve myelin antibodies may account for the segmental demyelination of the peripheral nerves occurring in this syndrome. Rising titers of complement-fixing anti-peripheral-nerve myelin antibodies have been found during the acute phase, and declining titers during convalescence[10]. The association of these antibodies with damage to myelin has been determined[10, 11].

Various methods of treatment have been advocated to modify the course of the disease. Supportive and symptomatic measures are still considered the mainstay of therapy. Steroid use was popular for many years, but controlled trials have found no benefit and corticosteroids can no longer be considered useful therapy[1]. For severe GBS plasmapheresis and high-dose intravenous immunoglobulin are other therapy methods. Plasmapheresis can shorten the duration of the disease and reduce the risk of respiratory failure if given early in the disease process. However, plasmapheresis is technically difficult to perform in children and may be contraindicated at any age because of cardiac instability, particularly for children less than two years old, and can be performed only in a few centers that have both the appropriate equipment and trained personnel[12]. When IVIG

therapy and plasmapheresis were compared in controlled trials, the functional recovery in the IVIG group was found to be more rapid and complete than in the plasmapheresis group. In addition, the mean period of intubation and hospitalization were found to be seven to 14 days less in the immunoglobulin group. These earlier studies showed that IVIG therapy is widely available, less aggressive, safe regarding viral transmission and adverse reactions, and less expensive[13, 14]. The rapid recovery of our patients was probably related to IVIG treatment.

The mode of action of IVIG remains uncertain, although several mechanisms have been proposed. Some evidence suggests that IVIG contains antiidiotype antibodies against the auto-antibodies present in patients with autoimmune diseases[15]. A similar action in GBS could be suspected, blocking the auto-antibodies against myelin present in these patients[10]. Alternatively, IVIG might improve neuronal damage by another mechanism. Approximately two-thirds of GBS cases follow an infection, and a virus or a bacterial toxin may be an etiologic factor. The IVIG may have provided neutralizing antibodies or antitoxin[1, 7].

Recently it has been reported that relapses may occur in GBS after treatment with IVIG. It is suggested that the active phase of the disease is longer than the duration of treatment in these individuals. In these patients longer treatment regimens might provide better results than current regimens[16, 17].

We conclude that immune globulin is a practical, safe and effective treatment for GBS. Because the condition is uncommon, multicenter, controlled studies are needed to evaluate this new method of treatment.

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LANGERHANS CELL HISTIOCYTOSIS ASSOCIATED WITH RECURRENT PNEUMOTHORAX*

A Case Report

*Ayşenur Ökten MD***, *Hilal Mocan MD****, *Erol Erduran MD*****
*Yakup Aslan MD******, *Halit R. Gümele MD*******, *Yavuz Özoran MD********

SUMMARY: Ökten A, Mocan H, Erduran E, Aslan Y, Gümele HR, Özoran Y. (Departments of Pediatrics, Pathology and Radiology, Karadeniz Technical University Faculty of Medicine, Trabzon, Turkey). Langerhans cell histiocytosis associated with recurrent pneumothorax: a case report. Turk J Pediatr 1986; 38: 125-130.

Pulmonary involvement of Langerhans cell histiocytosis (LCH) is an uncommon but important cause of pulmonary fibrosis and honeycombing in young adults. Rarely, pulmonary LCH may be complicated by spontaneous pneumothorax. It may be isolated or associated with multiple organ involvement. We describe here a case of LCH with diabetes insipidus, skin lesions and pulmonary involvement in a 15-year-old boy. The case was complicated by four episodes of spontaneous pneumothorax with typical radiologic findings of pulmonary LCH. His presentation, radiologic findings, treatment and clinical course during three-years of follow-up are discussed. *Key words: Langerhans-cell histiocytosis, recurrent pneumothorax.*

Eosinophilic granuloma of bone, Hand-Schüller-Christian disease and Letterer-Siwe disease constitute a complex of diseases of unknown cause. They are grouped under the term of histiocytosis X, now more correctly called Langerhans-cell histiocytosis (LCH)[1,2]. LCH has extremely variable presentations, and may be localized or disseminated[2].

Pulmonary involvement of LCH is uncommon and may rarely be complicated by spontaneous pneumothorax[3]. We present here a case of LCH with diabetes insipidus (DI), skin lesions and bilateral pulmonary involvement with honeycombing. This case was complicated by four episodes of spontaneous pneumothorax in the three-year follow-up period.

* From the Department of Pediatrics, Radiology and Pathology, Karadeniz Technical University Faculty of Medicine, Trabzon.

** Associate Professor of Pediatrics, Karadeniz Technical University Faculty of Medicine.

*** Professor of Pediatrics, Karadeniz Technical University Faculty of Medicine.

**** Assistant Professor of Pediatrics, Karadeniz Technical University Faculty of Medicine.

***** Research Assistant in Pediatrics, Karadeniz Technical University Faculty of Medicine.

****** Associate Professor of Radiology, Karadeniz Technical University Faculty of Medicine.

******* Professor of Pathology, Karadeniz Technical University Faculty of Medicine.

Case Report

A 15-year-old boy was admitted to our pediatric clinic with a six-month history of polyuria and polydipsia. His past history was unremarkable. Physical examination revealed a dozen discrete 1-2 mm reddish-brown papules on the trunk. No lymphadenopathy, hepatosplenomegaly, or respiratory difficulty was noted. His neurologic status was also normal.

Complete blood count and bone-marrow aspirate findings were normal. Skeletal survey showed no lytic lesions, and liver function tests were within normal limits. Immunologic testing revealed normal serum immunoglobulin levels. The number of circulating T-cells (E-rosette forming = 64%) were within normal limits, but the T_4:T_8 lymphocyte ratio (4.3) was very high, suggesting a deficiency of T_8-positive cells. The urinary volume was 3650 ml/m^2/day, and the water deprivation and arginine vasopressine tests were interpreted as neurogenic DI[2].

The chest x-ray displayed a "honeycomb" pattern (Fig. 1), and the most severe abnormalities identified on the pulmonary computerized tomography (CT) scan were cysts and nodules (Fig. 2). Magnetic resonance (MR) examination showed thickening of the pituitary stalk and absence of the normal hyperintense signal of the posterior hypophysis, which shows antidiuretic hormone supply of the hypophysis (Fig. 3).

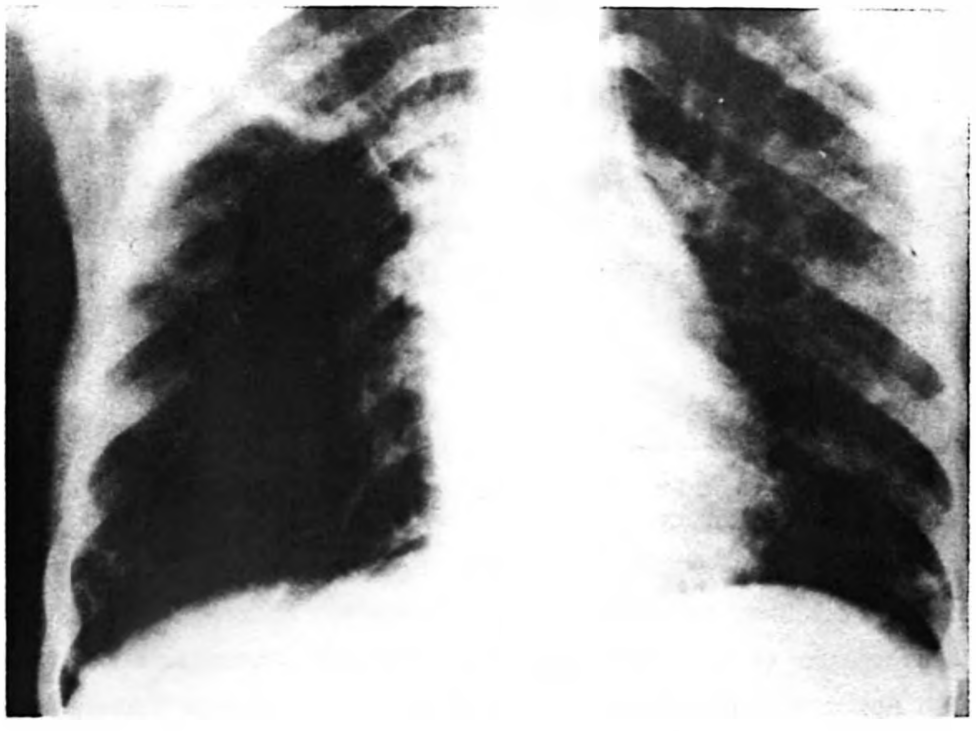

Fig. 1: Posteroanterior radiograph showing typical reticular, cystic and nodular abnormalities of pulmonary LCH, termed honeycomb pattern.

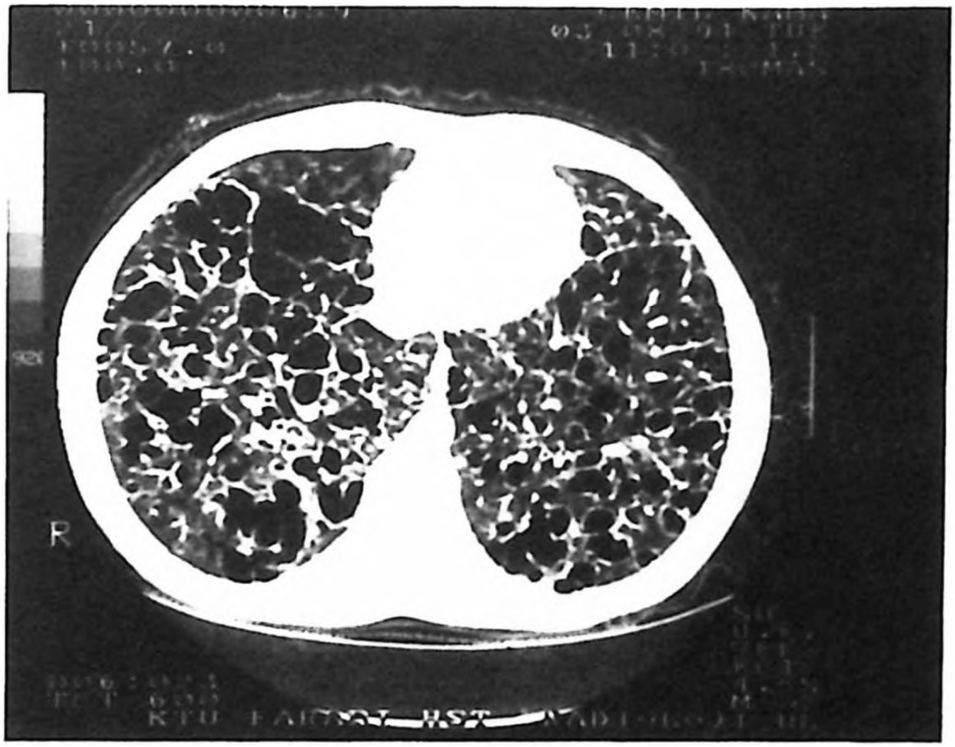

Fig. 2: CT scan showing cysts of various sizes with distinct, thin walls. Intervening lung tissue is normal.

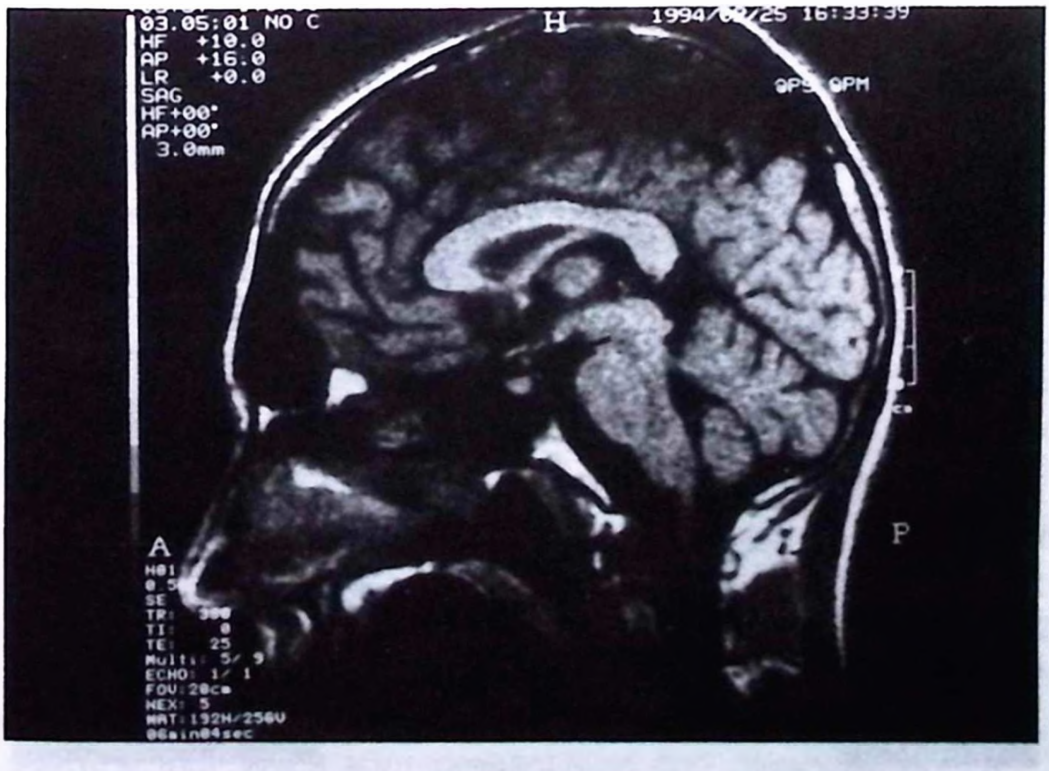

Fig. 3: MR examination showing thickening of the pituitary stalk and the absence of the normal hyperintense signal of the posterior hypophysis (arrow).

Forced vital capacity was reduced to 61 percent. The diagnosis of LCH was made by skin biopsy (Fig. 4) along with the other supporting clinical and laboratory findings.

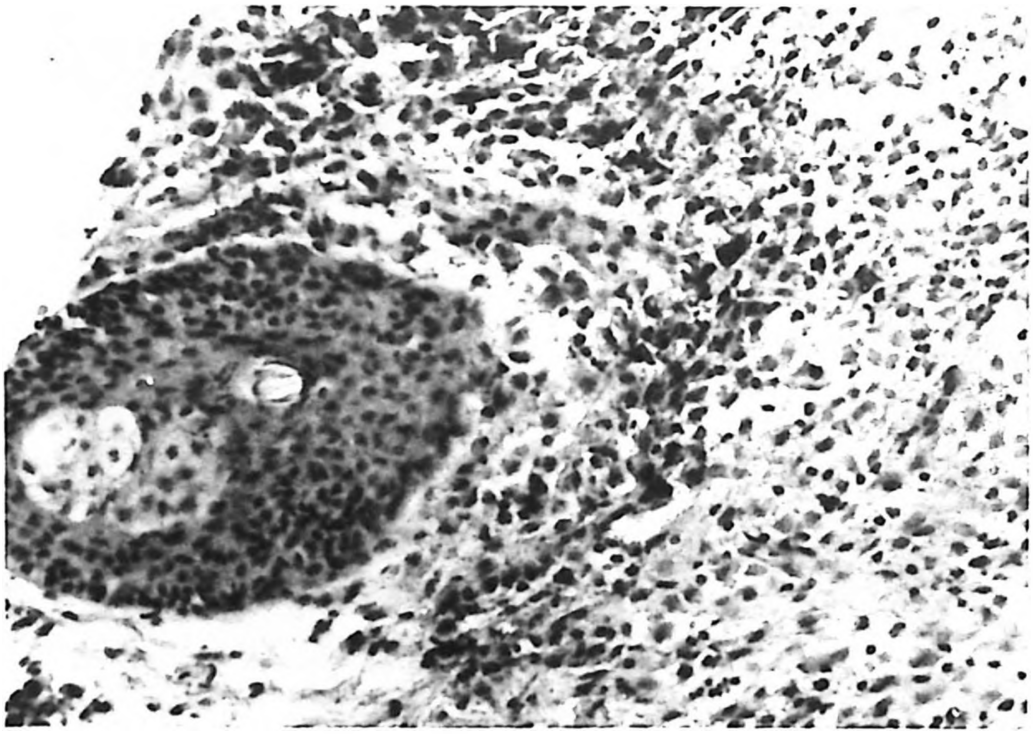

Fig. 4: The superficial dermal infiltrate consists of mononuclear histiocytes with indented nuclei.

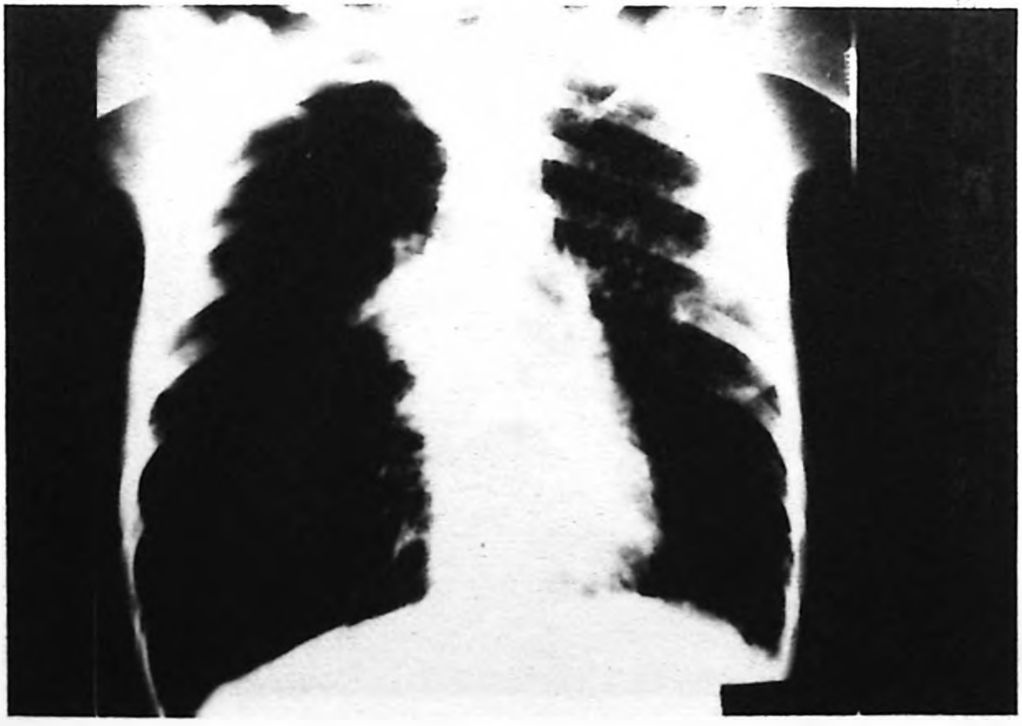

Fig. 5: Chest radiograph showing unilateral pneumothorax with typical findings of pulmonary LCH.

The patient was given a combination of arginine-vasopressine, prednisolone and vinblastine. Although prednisolone and vinblastine were discontinued three months after initiation of the therapy, arginine-vasopressine administration continued. Radiologic abnormalities of the pulmonary disease were not improved by the therapy, and the disease was complicated by four episodes of spontaneous pneumothorax which were treated with tube drainage during the three-year follow-up period (Fig. 5).

Discussion

Pulmonary involvement of LCH is an uncommon but important cause of pulmonary fibrosis and honeycombing in young adults[3]. It is suggested that 40 percent of patients with multisystem LCH have clinical and/or radiological evidence of lung pathology[4]. The most common functional disturbance is reduced lung or respiratory compliance with reduced lung volume and abnormal lung perfusion[4, 5]. In our case, vital capacity was found to be decreased. The main pathologic feature of pulmonary LCH is peribronchiolar inflammation leading to fibrosis and cyst formation. Although pulmonary LCH may be suspected on the basis of chest radiographic findings, the CT findings of predominantly upper lobe nodules and cysts are virtually pathognomonic[3, 5, 6]. All of these abnormalities were demonstrated in our case.

Diagnosis can be established by transbronchial or open lung biopsy[2]. However, Ha et al.[4] suggested that biopsy is unnecessary in most cases because lung involvement is often mild and transient and usually parallels overall disease activity. Lung biopsy should be considered when radiologic and clinical signs progress during follow-up[4]. We did not attempt an open lung biopsy because of the stable course of disease in our patient.

As pulmonary LCH progresses, the nodules decrease in number, leaving multiple thin-walled cysts. Rarely, cysts may be complicated by spontaneous pneumothorax. Januszkiewicz et al.[7] reported a case with three episodes of spontaneous pneumothorax due to pulmonary LCH. The present case was complicated by four episodes of spontaneous pneumothorax during the three-year follow-up period. Tube drainage was performed for each recurrence of spontaneous pneumothorax.

Pulmonary LCH may be isolated or associated with multiple organ involvement such as bone, hypothalamus, skin, etc[2]. Diabetes insipidus is a well-recognized component of LCH, with a reported prevalence of 5-50 percent in different series[8]. It is thought to be a result of infiltration of the posterior pituitary by Langerhans cells[9]. Only a few patients have DI on presentation with LCH, but it may develop during the first four years after presentation and diagnosis of LCH[9]. On MR examination, thickening of the hypothalamus and the pituitary stalk in the absence

of the posterior pituitary bright signal is seen in children with overt DI[10], as in our patient. Systemic drug therapy is generally offered only when there is complicating failure to thrive or gross organ dysfunction[5].

Treatment programs incorporate a variety of chemotherapeutic agents, including prednisolone, etoposide, methotrexate, cyclophosphamide and vinblastine[2]. It has not been possible to estimate a clear benefit from any particular treatment. The majority of cases resolve partially or completely, but some deteriorate[5]. Although in our case the lung function tests improved, radiologic improvement was not detected during prednisolone and vinblastine therapy, and the disease was complicated by four episodes of spontaneous pneumothorax.

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HENOCH – SCHÖNLEIN NEPHRITIS ASSOCIATED WITH SUBACUTE THYROIDITIS*

*Ayşe Öner MD***, *Gülay Demircin MD****, *Keriman Tınaztepe MD*****
*Ayşehan Akıncı MD******, *Tahsin Teziç MD*******

SUMMARY: Öner A, Demircin G, Tınaztepe K, Akıncı A, Teziç T. (Department of Nephrology, Dr. Sami Ulus Children's Hospital, Ankara, Turkey). Henoch-Schönlein nephritis associated with subacute thyroiditis. Turk J Pediatr 1986; 38: 131-135.

We present a 12-year-old boy who developed subacute thyroiditis during the course of rapidly progressive glomerulonephritis due to Henoch-Schönlein purpura (HSP) proven by clinical findings and percutaneous renal needle biopsy. The thyroid gland of the patient suddenly enlarged with mild tenderness while he was on steroid and dipyridamole therapy. Thyroid hormone levels revealed T_3 0.31 ng/ml (nl: 0.52-1.75 ng ml), T_4 2.53 ug/dl (nl: 4.8-12.8 ug/dl), free T_3 0.80 pg/ml (nl: 2.14-5.34 pg/ml), free T_4 0.2 ng/dl (nl: 0.73-1.95 ng/dl) and TSH 1.02 U/ml (nl: 0.36-3.25 U/ml). Antimicrosomal antibody was negative while antithyroglobulin antibody was slightly positive (1/80+). Hypoactivity with a spotty pattern was demonstrated by thyroid scanning. Serologically proven mumps infection was detected and may have been a triggering factor in the development of both HSP and subacute thyroiditis. *Key words: Henoch-Schönlein purpura, rapidly progressive glomerulonephritis, subacute thyroiditis, mumps.*

Henoch-Schönlein purpura (HSP) is a clinical syndrome of unknown etiology which is predominantly seen in childhood and is characterized by generalized vasculitis that affect small vessels[1]. Arthritis, gastrointestinal manifestations and nephritis usually accompany the characteristic skin lesions of HSP[2]. Clinical evidence of renal disease, the most serious feature of HSP, occurs in 20 to 75 percent of patients[1-2]. Involvement of other organs and systems such as the nervous system, eyes, endocrine glands and heart have rarely been reported in HSP[2-4], while thyroid involvement associated with HSP has not been reported before.

We present here a 12-year-old boy who developed subacute thyroiditis during the course of rapidly progressive glomerulonephritis (RPGN) due to HSP. The laboratory data revealed: Hb 17.8 g/dl, white blood cell count 23.200/mm^3 with 84% neutrophils and 16% lymphocytes. The erythrocyte sedimentation rate was 30 mm/hour. Urine examination showed 3 (+) proteinuria (6 g/m^2/day) and

* From the Department of Nephrology, Dr. Sami Ulus Children's Hospital, Ankara.

** Associate Professor of Pediatrics and Pediatric Nephrologist, Dr. Sami Ulus Children's Hospital.

*** Pediatrician, Dr. Sami Ulus Children's Hospital.

**** Professor of Pediatrics and Pediatric Pathologist, Hacettepe University Faculty of Medicine, Ankara.

***** Associate Professor of Pediatrics and Pediatric Endocrinologist, Dr. Sami Ulus Children's Hospital.

****** Professor of Pediatrics and Pediatric Endocrinologist, Dr. Sami Ulus Children's Hospital.

hematuria with granular casts. The serum sodium level was 119 mEq/L while the other electrolytes, renal and liver function tests were within normal limits. The creatinine clearance was 100 ml/min/1.73 m^2. The stool guaiac test was positive. Microbiological examinations were negative for a pathogen microorganism. Serum immunoglobulins and complement levels were normal. Abdominal ultrasonography revealed increased renal parenchymal echogenicity. The patient was treated with intravenous fluids for dehydration. On the third day of admission he was started on oral prednisolone therapy (60 mg/m^2/day) because of gastrointestinal system hemorrhage.

The patient developed scalp edema on the seventh day of hospitalization and hypertension on the tenth day. On the 11th day his renal functions were impaired with blood urea nitrogen 78 mg/dl, serum creatinine 2.8 mg/dl and proteinuria increased to 11 g/m^2/day. Percutaneous renal needle biopsy was performed, and endo- and extracapillary proliferative glomerulonephritis was demonstrated. The patient was given pulse therapy with methyl prednisolone on three consecutive days, and oral prednisolone (45 mg/m^2/day) was given together with dipyridamole and captopril on the following days. The steroid dose was tapered gradually after one month to a maintainence dose of 10 mg every other day.

On the 27th day, the patient's thyroid gland was diffusely enlarged with slight tenderness. He had also lost eight kilograms of weight during this time. Measurement of thyroid hormones revealed T_3 0.31 ng/ml (nl: 0.52-1.75 ng/ml), T_4 2.53 ug/dl (nl: 4.8-12.8 ug/dl), free T_3 0.80 pg/ml (nl: 2.14-5.34 pg/ml), free T_4 0.2 ng/dl (nl: 0.73-1.95 ng/dl) and TSH 1.02 U/ml (nl: 0.36-3.25 U/ml). Antimicrosomal antibody was negative while antithyroglobulin antibody was slightly positive (1/80+). Thyroid ultrasonography revealed diffuse glandular hyperplasia with enlarglement of the right lobe to 40 x 17 x 14 mm and left lobe to 40 x 14 x 13 mm. Scanning of the thyroid gland with Tc 99-m pertechnetate showed hypoactivity with a spotty pattern (Fig. 1). These clinical and laboratory data led to the diagnosis of subacute thyroiditis. Needle aspiration of the thyroid gland was performed, but adequate material could not be obtained to confirm the diagnosis. The patient was started on L-thyroxine therapy.

The serological tests performed five days after presentation of the first symptoms of subacute thyroiditis in order to find a viral etiological agent were negative for rubella, rubeola and Epstein Barr virus, while IgG for mumps was 1/10 (+) and increased to 1/40 positivity two weeks after the initial measurement.

Two weeks after therapy with methyl prednisolone, pulse renal function tests were normal and the proteinuria was decreased to 2 g/m^2/day. The patient's thyroid gland was diminished in 15 days and thyroid scanning returned to normal in three weeks with L-thyroxine treatment (Fig. 2). At the end of the third month, the proteinuria disappeared. In the sixth month the thyroid hormone levels were normal with T_3 1.47 ng/ml, T_4 10.25 ug/dl, free T_3 4.49 pg/ml, free T_4 1.27 ng/dl and TSH 1.43 U/ml.

The therapy with L-thyroxine and prednisolone was discontinued. In the seventh month the patient's antimicrosomal and antithyroglobulin antibodies were still normal. He was followed up for 22 months without any clinical or laboratory abnormalities.

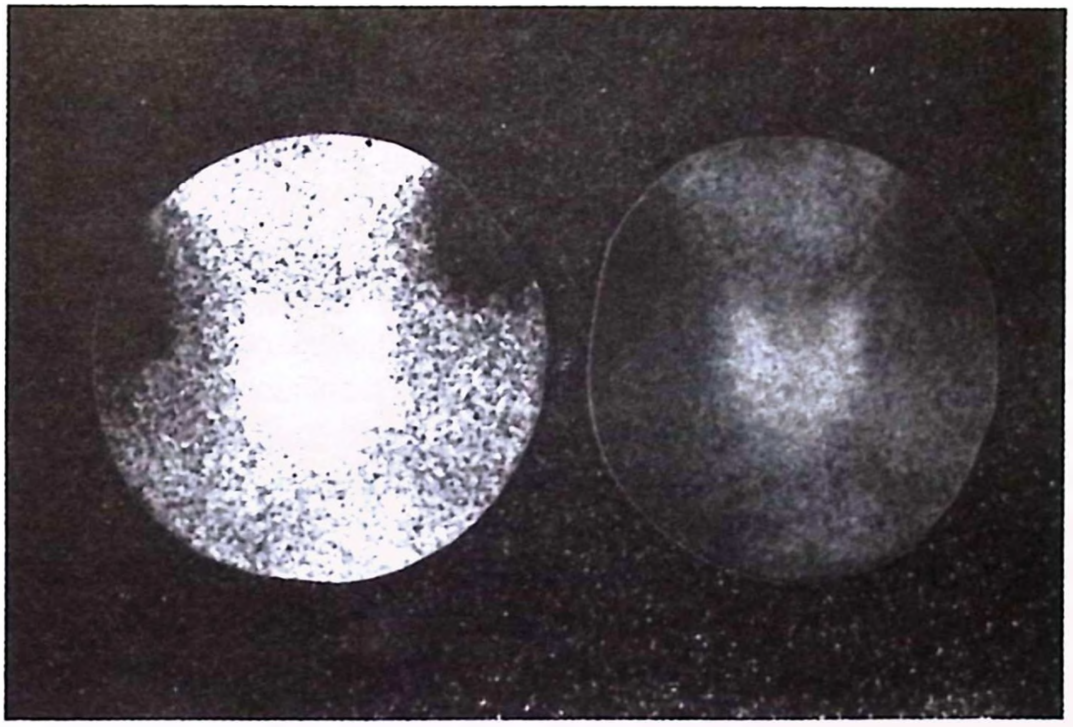

Fig. 1: Tc-99-m pertechnetate thyroid scanning demonstrates hypoactivity and spotty pattern in the gland.

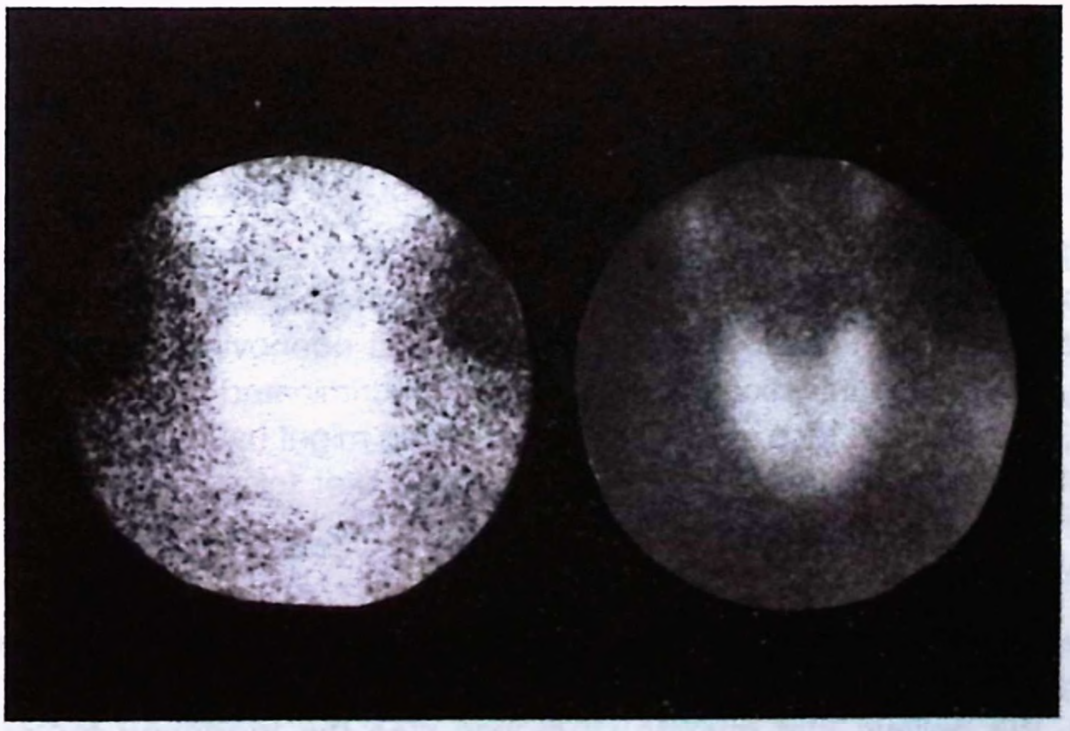

Fig. 2: Tc-99-m pertechnetate thyroid scanning shows normal thyroid gland after therapy.

Discussion

There are reports about the involvement of certain endocrine glands including the pancreas, adrenals, parotis glands and testes in HSP[2-4]. However, there is no report in the literature about thyroid pathology during the course of HSP. In this case report, a patient whose Henoch Schönlein nephritis was proven by characteristic clinical findings and percutaneous renal needle biopsy suddenly developed a diffuse, mildly tender goiter on the 27th day of steroid therapy, suggesting a diagnosis of thyroiditis. Development of symptoms under steroid therapy and tenderness of the thyroid gland with the findings on thyroid scanning suggested a diagnosis of subacute thyroiditis rather than autoimmune Hashimoto thyroiditis. The negative antimicrosomal antibody titers and slightly positive titer of antithyroglobulin antibodies which are increased significantly in 90 to 95 percent of patients with Hashimoto thyroiditis also supported the diagnosis of subacute thyroiditis[5]. Although we were not able to obtain adequate material for pathological diagnosis, the clinical improvement of the goiter, the disappearance of pathological findings on thyroid scanning in three weeks, and maintenance of clinical and laboratory remission long after therapy was discontinued confirmed the diagnosis.

Subacute thyroiditis is a self-limited, transient inflammation of the thyroid gland with a duration of one month to one year[5]. The thyroid gland is generally sensitive to palpation or only mildly tender[6]. It classically evolves through four consecutive phases: the hyperthyroidic phase lasting for 1-4 weeks, the euthyroidic, hypothyroidic and recovery phases[5, 6]. The thyroiditis of this patient was detected in the hypothyroidic phase when the thyroid gland was suddenly enlarged. The symptoms in the first two phases were masked by severe symptoms of Henoch Schönlein nephritis and by the effect of steroid therapy. Administration of prednisolone also inhibited the elevation of TSH which was expected to be high because of the positive feedback mechanism of low thyroid hormones[7].

Although the etiology of subacute thyroiditis remains unknown, identification of many patients with evidence of viral diseases such as mumps, coxsackie virus, influenza, measles, infectious mononucleosis and adenovirus suggests a viral etiology[5]. Since the infectious agents are also incriminated in the development of HSP, we searched for a single viral agent which might have triggered the HSP and subacute thyroiditis together. The initial IgG titer for mumps was found to be slightly positive, and increased significantly in two weeks, demonstrating that the patient had recently had mumps infection.

Review of the literature revealed eleven cases of thyroiditis in patients with serologically proven mumps, two cases of which grew mumps virus from thyroid tissue[5]. We believe that mumps virus was also the triggering factor in the developmenat of both HSP and subacute thyroiditis in this case. To our knowledge

this patient is the first in the literature to develop subacute thyroiditis during the course of HSP. The serologically proven mumps infection which might be the cause of the whole clinical picture would also support the infectious etiology in HSP and subacute thyroiditis.

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THE MEGACYSTIS – MICROCOLON – INTESTINAL HYPOPERISTALSIS SYNDROME*

Report of a Case and Review of the Literature

*Şule Yiğit MD***, *Çiğdem Barlas MD****, *Murat Yurdakök MD*****
*Lütfü Önderoğlu MD******, *Yeşim Zafer MD****, *İncinur Saltık MD****

SUMMARY: Yiğit Ş, Barlas Ç, Yurdakök M, Önderoğlu L, Zafer Y, Saltık İ. (Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). The megacystis-microcolon-intestinal hypoperistalsis syndrome: report of a case and review of the literature. Turk J Pediatr 1986; 38: 137-141.

The megacystis-microcolon-intestinal hypoperistalsis syndrome is part of a spectrum of intestinal motility disorders and is characterized by abdominal distension, lax abdominal musculature, incomplete intestinal rotation, microcolon, megacystis, bilious vomiting and decreased or absent intestinal peristalsis. In this report a newborn girl with megacystis-microcolon-intestinal hypoperistalsis syndrome is reported.
Key words: megacystis-microcolon-intestinal hypoperistalsis syndrome, prenatal diagnosis.

The megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS) is a congenital disorder characterized by urinary bladder distension and hypoperistalsis throughout the entire gastrointestinal tract. This uniformly fatal condition appears to be caused by functional disturbances of bladder and intestinal motility, for which a specific cause has not yet been recognized. The syndrome was first described in 1976 by Berdon et al[1]. Since then more than 40 cases with this syndrome have been reported in the medical literature[2], two of which were reported from Turkey[3,4]. We present a new patient with the megacystis-microcolon-intestinal hypoperistalsis syndrome with the aim of considering prenatal diagnosis of this rare syndrome.

Case Report

A twenty-nine-year old pregnant woman was referred to the maternity department of Hacettepe University Hospital at 33 weeks gestational age because of polyhydramnios. There was no consanguinity between the parents, who also had a nine-year-old boy with Down syndrome (47, XY, + 21) Ultrasonographic

* From the Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara.
** Pediatrician and Fellow in Neonatology, Hacettepe University Faculty of Medicine.
*** Research Assistant in Pediatrics, Hacettepe University Faculty of Medicine.
**** Associate Professor of Pediatrics, Hacettepe University Faculty of Medicine.
***** Associate Professor of Obstetrics and Gynecology, Hacettepe University Faculty of Medicine.

examination showed a large cystic structure in the fetal abdomen (Fig. 1). Because of accelerating polyhydramnios and respiratory distress of the mother, amniocentesis was performed twice to reduce the amniotic fluid volume.

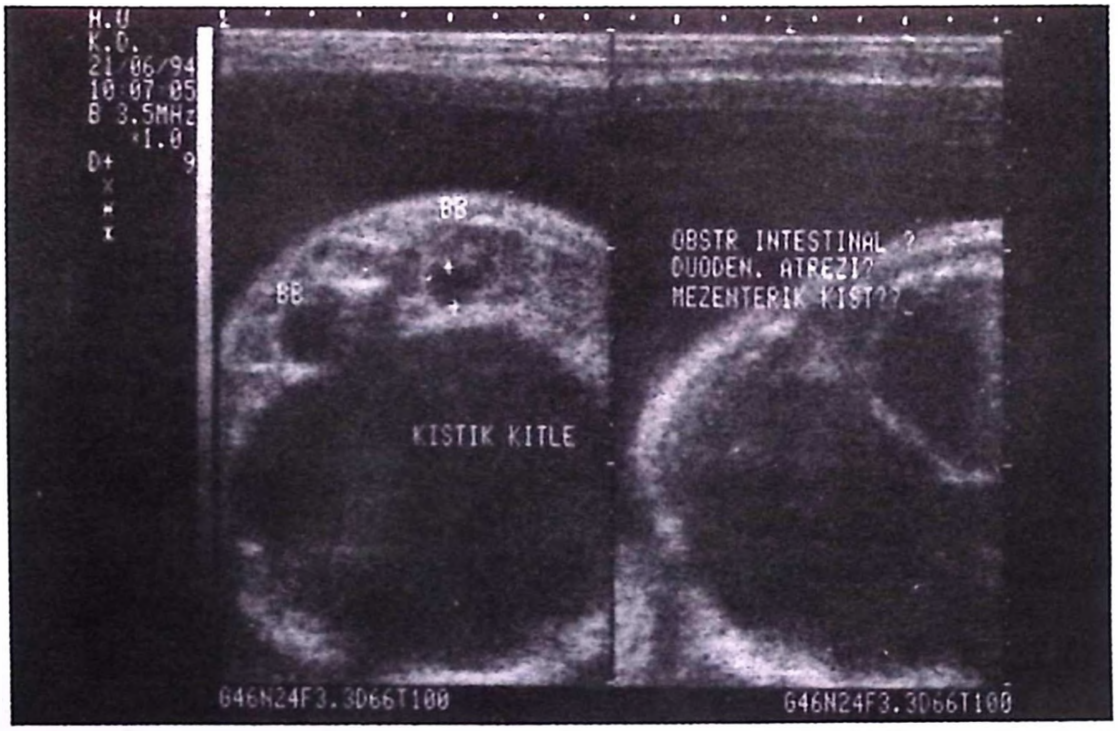

Fig. 1: Prenatal ultrasonographic appearance of large cystic structure in the fetal abdomen.

At 34 weeks gestational age a 2600 g female infant was delivered by cesarean section. The baby was noted to have marked abdominal distension and lax abdominal musculature. Most of the abdomen was occupied by a soft, slightly mobile mass. A plain radiograph of the abdomen showed a dilated stomach and no bowel gas, suggesting a high intestinal obstruction. Ultrasound examination demonstrated that the cystic mass was due to an enlarged bladder. The bladder was catheterized easily, and 700 ml of clear urine was obtained.

Intravenous pyelography and voiding cystourethrogram demonstrated a megacystic bladder without reflux (Figs. 2 and 3). There was pelvicalyceal and ureteral dilatation of the left kidney. Barium enema examination revealed microcolon (Fig. 4). The baby began to vomit bile-stained material on the first day of life. A nasogastric tube drained bilious fluid. No meconium was observed until three days after delivery, although a small rectal tube was inserted. Serum electrolytes, creatinine and BUN were found to be normal.

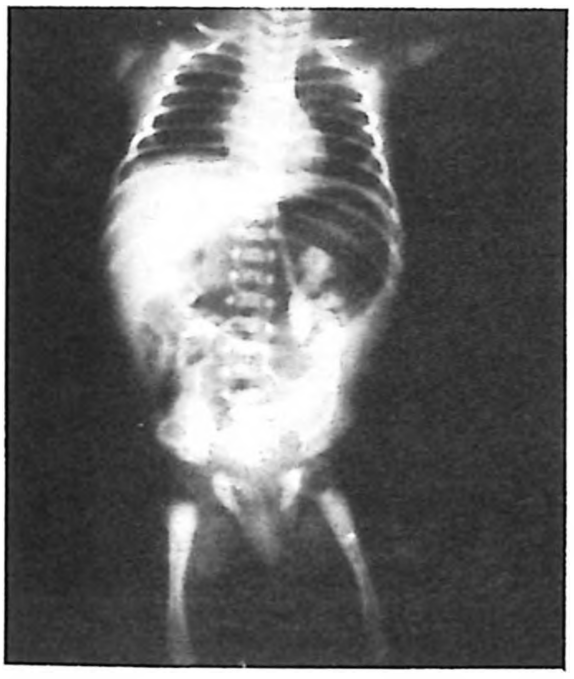

Fig. 2: The intravenous pyelography of the patient showing pelvicalyceal and ureteral dilatation of the left kidney.

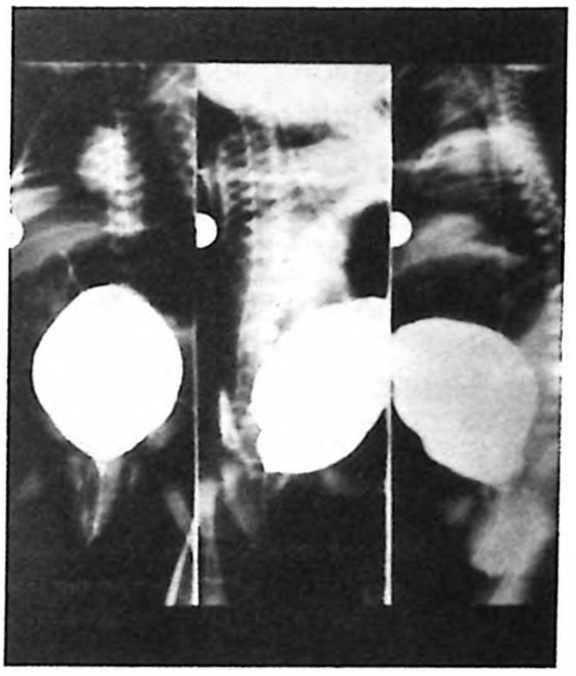

Fig. 3: The voiding cystourethrogram of the patient showing megacystic bladder without reflux.

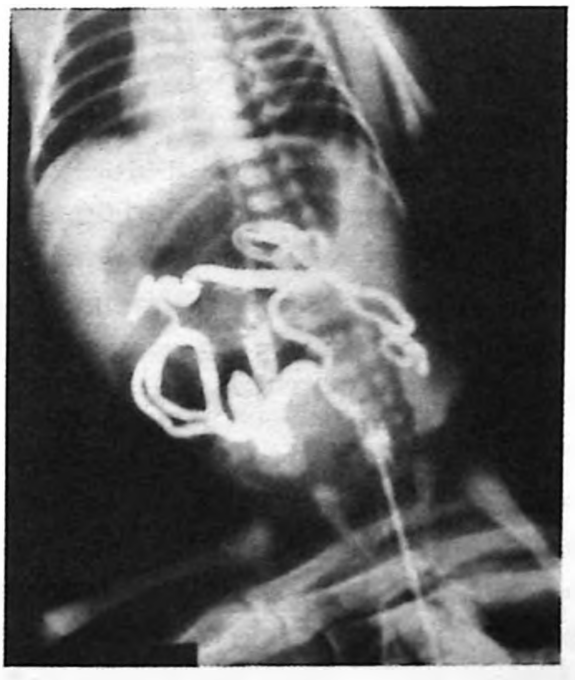

Fig. 4: The barium enema showing microcolon.

All these clinical and radiological findings suggested the diagnosis of MMIHS. Total parenteral nutrition via peripheral veins was initiated. Histological examination of the colon could not be performed. The patient was discharged from the hospital at the parents' request.

Discussion

Megacystis-microcolon-intestinal hypoperistalsis syndrome is part of a spectrum of intestinal motility disorders and is characterized by abdominal distension, lax abdominal musculature, incomplete intestinal rotation, microcolon, megacystis, bilious vomiting and decreased or absent intestinal peristalsis. It is generally incompatible with long-term survival, and death usually occurs within a year due to gram-negative septicemia. Rare cases surviving more than a year have been reported[5, 6]. Although there is a female preponderence, reports of male patients with MMIHS are increasing[7].

The etiology of this syndrome is unknown, but based on families with multiple siblings affected and consanguinity, autosomal recessive inheritance has been postulated[7, 8]. A relationship between maternal drug ingestion (clomiphene citrate, trimethoprim-sulfadiazine, dyprone, scopolamine) and MMIHS has also been suggested[3]. In the case of our patient there was no consanguinity or maternal drug ingestion, but the history of a sibling with Down syndrome was notable.

Similar to some of the cases reported in the literature[1, 5, 9-11], our patient's pregnancy was complicated by polyhydramnios. The etiology of polyhydramnios is unclear. It may be speculated that diminishing reabsorption of amniotic fluid from the intestine due to gastrointestinal dysfunction leads to polyhydramnios.

The pathophysiology and mechanism of the neuromuscular function disturbance in the gut and bladder remain unclear in this syndrome. While earlier reports have mentioned a full complement of normal mature ganglion cells in all parts of the bowel[5], recently inconsistent microscopic findings such as fewer and shrunk neurons in some parts of the bowel have been reported[12]. One of the most recent reports about the pathogenesis of MMIHS suggested that the intial event is an intramural inflammatory process that affects the gastrointestinal and urinary tracts[6]. Another new hypothesis is that MMIHS may be an unusual symptomatic form of neonatal axonal dystrophy[13].

Surgical intervention was not planned for the treatment and diagnosis of our patient. Since MMIHS represents a functional intestinal obstruction, surgical intervention has not been helpful and deaths due to septicemia in the post-operative period are frequent in patients with MMIHS[1, 3-5, 9, 14, 15]. Also, the disorder is resistant to pharmacotherapy[14]. Total parenteral nutrition is necessary for patients with MMIHS because of dysfunction of the gastrointestinal system.

Prenatal diagnosis of this condition by ultrasound gives information for appropriate investigation to be undertaken immediately after delivery. Prenatal ultrasound in subseguent pregnancies might reveal an enlarged bladder in early pregnancy, and a selective termination may be an alternative[2]. Our patient's sonographic examination revealed megacystis, mild left hydronephrosis and polyhydramnios.

Similar findings may lead to the diagnosis of MMIHS. Prenatal diagnosis of this syndrome by ultrasound has been reported as early as 16 weeks of gestation[8]. Therefore, in high risk cases any change in the urinary collective system should perhaps be considered to be a sign of MMIHS.

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