Maple syrup urine disease-treatment and outcome in patients of Turkish descent in Germany

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Maple syrup urine disease (MSUD) is a rare autosomal recessive disorder that causes acute and chronic brain dysfunction because of a neurotoxic effect of the accumulating branched chain amino acids (BCAA) and their corresponding keto acids.

Aim of the treatment is a rapid reversal of the neonatal decompensation and a stable long-term metabolic control obtained by a carefully adjusted BCAA-low diet.

In optimally treated patients, an unimpaired neurological and intellectual outcome is possible. Ten patients of Turkish origin suffering from MSUD are presently treated in the Metabolic Unit of the University Hospital in Düsseldorf, Germany. All patients show mild intellectual deficits; neurological impairment is rare. This paper aims to define the feasible standard of therapy and the resulting intellectual and psychosocial outcome achievable in MSUD patients of Turkish origin under high standard conditions of medical care for inborn errors of metabolism.

Key words: maple syrup urine disease (MSUD), treatment, outcome, intelligence.

Maple syrup urine disease (MSUD) is a rare autosomal recessive inborn error of metabolism that causes acute and chronic brain dysfunction. In the autochthonic German population, the frequency is estimated to be 1 in 500,000; in populations with a high rate of consanguineous marriages, such as in Turkey, the incidence is notably higher and may be as high as 1 in 50,000 newborns (Dursun, personal communication).

Maple syrup urine disease is due to mutations in the three different gene loci encoding the E1α, E1β and E2 subunits of the mitochondrial branched-chain 2-keto acid dehydrogenase (BCKDH) complex. Mutations result in a deficient capacity to further degrade the 2-keto acids formed in the catabolic pathway of the branched-chain amino acids (BCAA) valine, leucine and isoleucine[1]. The metabolic block results in markedly increased plasma and tissue concentrations of leucine, valine, isoleucine and allo-isoleucine as well as their 2-keto acid analogues. Especially leucine and its transamination product, 2-keto isocaproate (KIC), are thought to exert neurotoxic effects in high concentrations, leading to acute and chronic brain dysfunction.

Newborns with severe classic MSUD are asymptomatic at birth but develop serious symptoms from the fourth day of life, when rising blood levels of leucine and KIC surpass critical concentrations and initiate neurotoxic effects. Symptoms include lethargy, decreased feeding and progressive neurological signs of alternating muscular hypotonia and hypertonia with dystonic extensions of the arms, a bulging fontanel due to cerebral edema and seizures. There is a rapid progression to coma. With onset of symptoms the newborns start to emit an intensive caramel-like odor resembling maple syrup.

Most infants have reached a acritical comatose state when MSUD is first suspected, which is usually the case after 10 days of life. At that time the plasma leucine concentration ranges between 2.5 and 4.5 mmol/L, which is greatly increased (normal: <150 μmol/L). In order to reverse the acute intoxication, the patients are

in need of rapid removal of the branched-chain compounds by extraneous measures such as peritoneal dialysis, blood exchange transfusion, hemodialysis and hemofiltration[2].

Once the children have passed this critical condition, they are in need of a permanent reduction of the dietary intake of leucine, valine and isoleucine in order to keep the plasma BCAA levels close to normal. For that the amount of natural protein has to be highly restricted, and great amounts of a special protein substitute in the form of leucine-, valine- and isoleucine-free amino acid mixtures are necessary. Frequent checks of the blood BCAA levels are essential in order to titrate the BCAA intake against the plasma concentrations. Discontinuation of the diet as well as febrile illnesses resulting in an increase of catabolism and amino acid release from muscle protein can precipitate severe metabolic decompensation at any age leading to acute encephalopathy, which deserves emergency treatment. Unless treatment is started early, severe permanent brain damage or death occurs within the first months of life.

There is evidence that in patients with classic MSUD the intellectual outcome is

1. inversely related to the duration of high plasma leucine levels during the neonatal illness[3-6] and
2. inversely related to the longitudinal plasma leucine concentrations in childhood being an indicator of the quality and compliance of dietary treatment[7].

This paper aims to define the feasible standard of therapy and the resulting intellectual and psychosocial outcome in MSUD patients of Turkish origin under high standard conditions of medical care for inborn errors of metabolism.

Material and Methods

Of the 78 known MSUD patients living in Germany, 32 are of Turkish decent. Ten of these patients (3 male, 7 female) aged 3 to 30 years are followed in the Metabolic Center of the University Hospital Düsseldorf. Nine suffer from a classic severe form of MSUD and one has a severe variant form with a less serious neonatal presentation who nevertheless is in need of a strict diet as in the classic form. All patients are treated with a diet that contains defined quantities of BCAAs and which is regularly controlled by measuring the levels of the BCAAs in plasma.

The details of the patients' initial illness and the long-term metabolic (biochemical) control as well as data on the intellectual and psychosocial (schooling, professional career) outcome were obtained retrospectively from the case notes. For each patient the annual median values of all quantitative plasma leucine determinations were calculated.

Psychometric tests were performed in the course of the long-term monitoring at different times. As testing was not performed in the course of a study, it is obvious that there are different examiners, no consistent age and diverse methods of testing. All test systems used were non-verbal to avoid differences in performance because of language difficulties. IQ tests used were two versions of the non-verbal Snijders Oomen intelligence test (S.O.N. 2.5-7, S.S.O.N. 7-17) for children of different ages, the Kaufmann-ABC Battery and the TBGB Testbatterie for geistig behinderte Kinder (Battery for mentally handicapped children).

Results

All patients were born in Germany to consanguineous parents. In most families there was no known history of metabolic diseases; however, in two families frequent deaths of unknown cause had occurred. In one family a pregnancy had been aborted after a fetus affected with MSUD was identified by prenatal diagnosis.

In seven patients mutational analysis in the three genes coding for the BCKDH complex was performed. All patients showed homozygous mutations. In four cases the E1β gene was affected; in two cases a mutation in the E1α- and the E2-gene, respectively, was found. One patient had two homozygous mutations, one in the E1β- and one in the E1α-gene (Table I).

Table II provides information on the neonatal illness. All nine patients suffering from a classic form of MSUD were diagnosed in their second and third week of life (between days 9 and 17, mean day 13). The clinical findings at that time were rather uniform: All patients showed typical neurological symptoms and were comatose. In all patients a strong maple syrup-like odor of the urine was noted. The peak plasma leucine concentration ranged from 2.1 to 4.2 (mean 3.15) mmol/L. All patients were in need of extracorporal toxin removal. Eight

received blood exchange transfusions; one patient was hemofiltrated. The postnatal period during which the plasma leucine level remained above 1 mmol/L ranged from 11 to 19 days for eight patients, and was delayed to 34 days in patient 9 due to improper treatment. Patient 10 suffers from a non-classic variant MSUD with a comparatively late and less severe neonatal manifestation without coma, moderate increase of plasma leucine (diagnosis on day 21, peak level: 1214 µmol/L) and no need for extracorporal toxin removal.

Table I. Demographic Data and Mutations

Patient no.	Sex	Present age (yrs; mos)	Parental consanguinity	Family history	Affected locus	MSUD alleles
1	F	3;5	+	None	E1β	Homozygous K222R
2	M	5;2	3rd cousins	Several siblings of the father died as neonates of unknown cause	E1β	Homozygous Y383X
3	F	7;6	+	None	E2	homozygous A314 K339 del
4	M	11;9	+	None	E1β	homozygous R285X
5	F	12;6	1st cousins	None	No mutational analysis performed	
6	F	19;5	1st cousins	None	E1α	homozygous Y383X
7	M	21;2	1st cousins	None	No mutational analysis performed	
8	M	22;7	1st cousins	1990 prenatal diagnosis; Fetus with MSUD aborted Uncle mentally disabled	E1β E1β	homozygous T151M homozygous V251A
9	F	29;4	+	Older siblings died as neonates of unknown cause	No mutational analysis performed	
10	F	30;9	+	None	E1α	homozygous G290R

P: female, M: male, MSUD: maple syrup urine disease.

Table II. Neonatal Presentation

Patient no.	Age at diagnosis (days)	Clinical history before diagnosis	Peak leucine level (µmol/L)	Toxin removal procedure	First day PL <1 mmol/L (days)
1	11	Poor feeding, seizures, axial hypotonia, Limb hypertonia, coma	3471	Exchange transfusion	17
2	15	Poor feeding, muscular hypotonia, coma	4237	Exchange transfusion	19
3	13	Poor feeding, opisthotonus, coma, specific odor	2518	Exchange transfusion	16
4	11	Poor feeding, muscular hypotonia, seizure, coma, apnea	2136	Exchange transfusion	16
5	15	Opisthotonus, seizures, coma	2560	Hemofiltration	17
6	14	Poor feeding, muscular hypertonia, seizures, coma	3344	Exchange transfusion	16
7	9	Poor feeding, opisthotonus, muscular hypotonia, Specific odor, coma	3794	Exchange transfusion	11
8	17	Poor feeding, seizures, coma	3618	Exhange transfusion	19
9	13	Apathy, poor feeding, muscular hypotonia, coma	2700	Exchange transfusion	34
10	21	Day 18 apathy, reduced spontaneous movements, Abnormal newborn screening for MSUD	1214	None	23

PL: Plasma leucine.

For every patient the annual medians of plasma leucine values are shown in Figure 1. The frequency of checking the plasma amino acids profile decreased with advancing age: in the first year of life there was an average of 75 measurements, at the age of six the average number of checks was 30, going further down to 20 to 10 checks during the teenage period. In late adolescence/adulthood the frequency of BCAA checks was sometimes only twice a year (data not shown).

Table III provides the results of psychological testing and details about schooling and professional education as well as the present circumstances of life. Using the Wechsler classification (for definition see Table II), two patients showed an intelligence in the low-average range, two patients were borderline and four showed mild mental retardation. Four adult patients had finished school for the mentally handicapped without diploma, and one patient graduated from a secondary school.

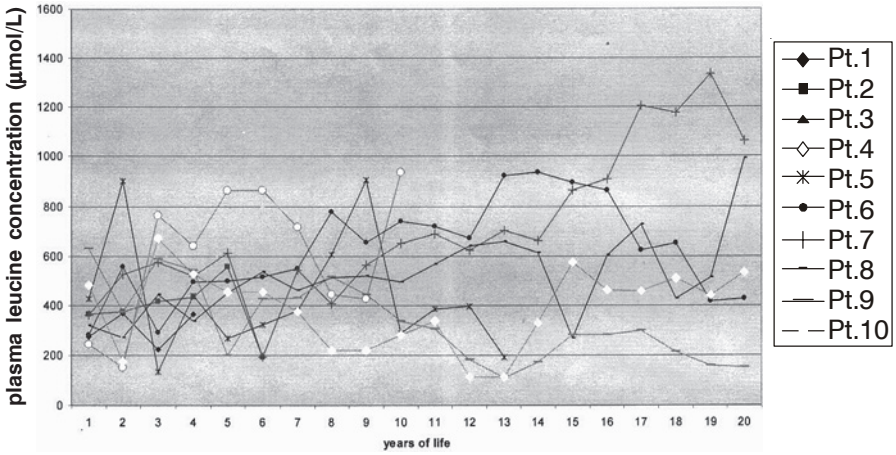

Fig. 1. Supported by the German BMBF (Ministry of Research) as part of METABNET.

Table III. Intellectual Outcome

Patient no.	Age (years) at testing, mode of testing, IQ-score	Schooling and professional education present circumstances
1	no testing performed	
2	4;11y, SON-R 2.5-7, IQ 86	
3	5;4y, SON-R 2.5-7, IQ 50 6;2y, SON-R 2.5-7, IQ 50,	No primary school
4	4;7y, SON-R 2.5-7, IQ <55	Normal primary school
5	5y, SON-R 2.5-7, IQ 75 7y, K-ABC, IQ 83	School for learning disabled
6	13; 1y: IQ 75	Gradulated from secondary school, no vocational training Presently: course of studies in Islamic theology
7	14;2y, SON-R 5.5-17, IQ<55	Finished school for mentally handicapped, no vocational training Presently: works as a help in a bakery
8	no testing performed	Finished school for mentally handicapped Works in a sheltered workshop
9	6;11y, TBGB, IQ 72	Finished school for mentally and physically handicapped No vocational training, presently: works in a sheltered workshop
10	11;6y, SON-R 5.5-17, IQ 61	Finished school for mentally handicapped, no vocational training Married, mother to a healthy daughter, housewife

IQ: Intelligence Quotient, y: years, SON-R 2.5-7: Snijders Oomen Non-Verbal Intelligence Test for children between 2.5 and 7 years, SON-R 5.5-17: Snijders Oomen Non-Verbal Intelligence Test for children between 5.5 and 17 years. K-ABC: Kaufmann-ABC Battery, TBGB: Testbatterie für geistig behinderte Kinder (Battery for mentally handicapped children). Definitions of Intelligence using Wechsler Intelligence Scale: IQ scores 89-110, average; 79-88, low-average; 68-78, borderline; <67, intellectual deficit.
Definitions of the range of mental retardation: IQ scores 50-70, mildly retarded; 35-50, intermediate; 20-35, severely retarded.

None finished school with university entrance diploma. No patient entered normal professional life. The adults are presently doing unskilled labor jobs, work in sheltered workshops or are unemployed without ever having initiated a professional training.

Discussion

Presently 1.87 million Turks live in Germany, which is approximately 4.4% of the population. Particularly in North-Rhine Westphalia, where Düsseldorf is located, the number of persons of Turkish descent is exceptionally high due to the influx of a great number of guest workers into this densely industrialized area in the 1960s. Turkey has a high rate of consanguineous marriages, reaching 40% in some rural areas in the eastern parts of the country[8], where the majority of the Turks living in Germany are from. The rate is believed to be equally high among people of Turkish origin living abroad[9]. In our patients, parental consanguinity was 100%, which is even higher than the 84% presumed for MSUD patients in Turkey. The high rate of consanguinity is reflected by the exclusively homozygous mutations we found in the three MSUD genes in our Turkish patient group.

Diagnosis of MSUD is usually made between 10 and 20 days of life after the patient has already been in coma for a couple of days. Interestingly, there has been no advance in time of diagnosis of MSUD in Germany during the last three decades despite increased awareness of pediatricians of autosomal recessive metabolic disorders in Turks and other population groups with high rates of consanguinity. However, obviously there has been an improvement in knowledge of how to treat newborns with MSUD in the seven years between the diagnosis of patients 9 and 8 resulting in a shorter period of neonatal decompensation.

A remarkable success with respect to diagnosis of MSUD from among many other inborn errors of metabolism was the introduction in 2002 of the tandem mass spectrometry-based newborn screening in Germany. If the screening procedure is properly applied (blood prick at 36 hrs of life, sending the filter paper blood to a newborn screening laboratory by overnight mail without delay, biochemical testing on the same day), the tentative diagnosis of MSUD should be possible by day 5, and thus sufficiently early for an adequate intervention in a still pre-symptomatic newborn. In those patients, the increased leucine blood levels could be decreased to a non-toxic range within 24 to 48 hrs without extracorporal detoxification, which strongly decreases the risk of brain damage during the particularly vulnerable neonatal period.

The severity of the neonatal crisis with the risk of brain damage depends on the knowledge of the medical staff and cannot be influenced by the patient's family. However, family members do well determine the extent of brain dysfunction which may arise during childhood due to high BCAA concentrations as a consequence of poor compliance with the daily diet. Upon review of the annual medians of plasma leucine levels of the different patients in Figure 1, it become obvious that a stable metabolic control with low leucine concentrations over long periods is feasible when a strict diet is kept. This is the case in young children who are strictly following the treatment protocol because of a rigid supervision by their parents. During late childhood, plasma leucine concentrations tend to rise, presumably because schoolchildren and adolescents spend more and more time outside the family. With advancing independence, the compliance with the diet becomes poorer because the patient himself often does not abide by the instructions of treatment. Among the youngest patients, it is obvious that in patient 3 (unlike patient 2), the already high leucine levels in the preschool age are due to the parents' inability to maintain a proper diet and frequent monitoring despite endless explanations and admonitions by the medical team. The parents did not realize the significance of the "invisible" disorder and did not want to strain and annoy the child with a diet and frequent consultations in the hospital. Patient 9 can be taken as an example of a patient with a satisfactory leucine level. Due to insufficient treatment during the neonatal period, the patient suffers from spasticity and impaired mobility due to which she has no independent access to food and therefore has maintained a satisfactory stable leucine level nearly all her life.

In all studies concerning outcome in MSUD, intellectual deficits in the patients in comparison to their healthy siblings and parents have been observed[4,10,11]. An unimpaired outcome is rare, and all Turkish patients followed in the Düsseldorf Metabolic Center

show impaired intelligence, ranging from low-average via borderline intelligence to mild mental retardation. Since no intellectual screening of parents and non-affected siblings of the patients was performed, there is no information available about possible familial influences on intelligence.

In summary, all the clinically diagnosed patients of Turkish origin suffering from MSUD show an impairment of intellectual development of varying degrees, but no problems of social integration and adaptation. Permanent neurological impairment is rare: only one patient suffers from spasticity making it impossible to live independently.

To recapitulate, we could show that the widespread belief among medical professionals in Turkey that MSUD results in death during infancy or severe neurological defects in surviving patients is erroneous. Today the vast majority of MSUD patients survive the neonatal crisis and infancy, and severe neurological or intellectual impairment is preventable. At least in countries with high standard care for metabolic disorders, the patients reach adult hood showing mild intellectual deficits without serious impairment of independence and with an adult social life, including marriage and having children. As an unimpaired outcome of the disease has been proven possible, the necessity of early diagnosis and optimal treatment cannot be overemphasized. Furthermore, it is extremely important to maintain an optimum metabolic control by frequent measurements of plasma BCAA and a constant supervision and training regarding diet management.

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