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# FREQUENCY OF CARDIOVASCULAR AND GASTROINTESTINAL MALFORMATIONS, LEUKEMIA AND HYPOTHYROIDISM IN CHILDREN WITH DOWN SYNDROME IN TRABZON, TURKEY*

*F. Müjgan Aynacı MD***, Fazıl Orhan MD***, Figen CELEP MD****
*Ahmet Karagüzel MD*****

**SUMMARY: Aynacı FM, Orhan F, Celep F, Karagüzel A. (Deparments of Pediatrics and Medical Biology, Karadeniz Technical University Faculty of Medicine, Trabzon, Turkey). Frequency of cardiovascular and gastrointestinal malformations, leukemia and hypothyroidism in children with Down syndrome in Trabzon, Turkey. Turk J Pediatr 1998; 40: 103-109.**

**This study was carried out to determine the frequency of congenital heart defects, cholelithiasis, hypothyroidism and leukemia in 31 children with Down syndrome. Twenty children (71.4%) had congenital heart defects. Ultrasonography was performed on 29 and two of these (6.9%) had cholelithiasis. Tests for hypothyroidism in 24 children identified hypothyroidism in three (12.5%). Leukemia was diagnosed in three children (10%) (one with congenital, two acquired). One patient with congenital hypothyroidism underwent surgery on the third day of life because of annular pancreas and duodenal atresia.** *Key words: Down syndrome, congenital heart defect, hypothyroidism, cholelithiasis, annular pancreas, leukemia.*

The presence of an extra chromosome 21 results in the best recognized and most frequent human chromosomal syndrome, Down syndrome[1]. Worldwide, the prevalence of Down syndrome is 1 in 700 births and boys outnumber girls 1.3 to 1.0[1-4].

Ophthalmic problems (refractive error, strabismus, nystagmus, cataracts, blepharitis and keratoconus), hearing loss (60 to 90% of the children), dental or oropharyngeal problems, skin problems (thin hair and sensitive skin), congenital heart diseases, and endocrine and musculoskeletal abnormalities (hypotonia, joint laxity, joint dislocations) have all been described in Down syndrome[1-18].

In this report, hypothyroidism, cholelithiasis, and cardiac and hematologic abnormalities were investigated in 31 children with Down syndrome.

* From the Departments of Pediatrics and Medical Biology, Karadeniz Technical University Faculty of Medicine, Trabzon.

** Associate Professor of Pediatrics, Karadeniz Technical University Faculty of Medicine and Fellow in Pediatric Neurology, Hacettepe University Faculty of Medicine, Ankara.

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

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

***** Professor of Medical Biology, Karadeniz Technical University Faculty of Medicine.

## Material and Methods

This study was carried out in 31 children (16 boys, 15 girls) with Down syndrome admitted to the Pediatrics Department of Karadeniz Technical University Faculty of Medicine, Trabzon. The patients were aged between four hours and 15 years (mean 44.2 ± 21.2 months).

Chromosomal studies were carried out on cultures of peripheral blood lymphocytes and metaphase smears were prepared by standard procedures.

According to the results of the chromosomal analysis, echocardiographic investigation for heart defects was necessary in 28 cases (93.3%). Thyroid hormones ($T_3$, $T_4$, TSH, free $T_3$, free $T_4$) were tested in 24 children (80%) for hypothyroidism. Ultrasonographic examination was made in 29 patients (96.6%) for cholelithiasis. All of the patients were evaluated for leukemia.

Standard radioimmunoassay procedures were utilized for the determination of $T_4$ and TSH levels in serum. In the newborn period, hypothyroxinemia was defined as a $T_4$ level < 2 SD of the mean at the time of the testing period. Hyperthyrotropinemia was defined as a TSH level > 20 μU/ml. Persistent primary hypothyroidism was defined as hypothyroxinemia with concomitant hyperthyrotropinemia on the confirmation testings, with or without clinical symptoms.

## Results

Twenty patients (96.7%) had classic trisomy 21. Translocation was detected in one case.

Twenty children (71.4%) had congenital heart defects including ventricular septal defect (VSD), atrial septal defect (ASD), mitral insufficiency (MY), Fallot tetralogy (FT), endocardial cushion defect and patent ductus arteriosus (PDA) (Table I). In the neonatal period and during childhood, ASD was found to be the most common heart defect (75% and 40%, respectively).

Table I: Congenital Heart Defects in 20/28 Children with Down Syndrome

| | Patient | | Sex | |
|---|---|---|---|---|
| Heart Defect | No. | % | Female | Male |
| ASD | 8 | 40 | 3 | 5 |
| VSD | 6 | 30 | 3 | 3 |
| MY | 2 | 10 | – | 2 |
| ASD ± VSD | 1 | 5 | – | 1 |
| Tetralogy of Fallot | 1 | 5 | 1 | – |
| Endocardial cushion defect | 2 | 10 | 1 | 1 |
| Total | 20 | 71.4 | 8 | 12 |

ASD: Atrial septal defect. VSD: Ventricular septal defect. MY: Mitral insufficiency.

Of the 24 cases tested for hypothyroidism two had congenital hypothyroidism and one had acquired hypothyroidism. Annular pancreas and duodenal atresia were identified in the first patient with hypothyroidism, and surgery was performed on the third day of life. The second patient had congenital leukemia associated with hypothyroidism. The third patient was an eight-month-old male. Therapy of thyroxin was started in all three patients.

Cholelithiasis was found in two of the 29 children (15 boys, 14 girls) examined by abdominal ultrasonography. These cases were 25-day-old and 11-month-old male patients. No symptoms were present in either of the patients which suggested cholelithiasis.

Leukemia was identified in three patients. The first patient was a four-hour-old male, admitted to our clinic with symptoms and signs of bleeding, hepatomegaly (4 cm) and splenomegaly (7 cm). Peripheral blood smear revealed 45 percent blastic cells; bone marrow and flowcytometric examination were consistent with $M_2$ leukemia. He died eight days after admission. The second patient was a one-and-a-half-year-old male. He was followed as $M_5$ leukemia and died one and a half years after chemotherapy. The third patient had $L_1$ type of acute lymphoblastic leukemia (ALL) diagnosed at 14 years of life and has been followed up with chemotherapy. Physical and laboratory examination of these patients revealed hepatosplenomegaly and anemia.

## Discussion

In previously unsuspected cases, the diagnosis of Down syndrome usually can be made at birth on the basis of the physical examination. The infant has microcephaly, with flattening both of the occiput and face; the nose is low and there is an upward slant of the eyes with epicanthal folds. Eyes often have speckled irides (Brushfield spots). The ears and mouth are small, but tongue is large. The joints are hyperextensible. The hands and fingers are short and broad. The fifth finger shows clinodactyly[1,2,5]. A single palmar crease often appears on the palms. Most children with Down syndrome have dermatologic problems such as thin hair, sensitive skin and alopecia[2,9]. In addition, there is a high prevalence of ophthalmic findings such as strabismus (50%), nystagmus (35%), cataracts (3%), blepharitis and keratoconus[2]. Suyugül et al.[11] evaluated eye findings of 44 cases with Down syndrome. They observed slanting palpebral fissures (88.6%), epicanthus (47.7%), blepharitis (9.0%), Brushfield spots (38.6%), peripheric iris hypoplasia (40.9%), strabismus (3.8%) and myopia (35.8%).

Ninety-four percent of cases with Down syndrome are due to non-disjunction, three percent to parental translocation (usually 14/21) and three percent to mosaicism[12,14]. In Turkey, Balcı[5] found that 93.6 percent of 1000 cases with

Down syndrome were due to regular type, 6.2 percent to translocation and 0.5 percent to mosaicism. In our study, the rate of 96.6 percent regular type was compatible with literature.

The most common medical problems in the newborn period result from congenital heart disease (CHD) and intestinal blockage. Approximately 40 to 50 percent of children with Down syndrome are born with CHD[16]. Most commonly an endocardial cushion defect, other cardiac defects include tetralogy of Fallot, atrial septal defects, PDA and VSD[16]. In a prospective study to determine the incidence of cardiovascular malformations in neonates with Down syndrome, 50 percent of babies had CHD. The most common cardiac anomaly was VSD (41.1%) and with decreasing frequency, others were PDA (17.6%), ASD (11.8%), ASD and PDA (11.8%), hypertrophic cardiomyopathy (5.9%), hypertrophic obstructive cardiomyopathy (5.9%), and complex cyanotic heart disease (5.9%)[8]. In our study, eight cases were newborn and four out of five of babies (80%) had CHD (75% ASD, 25% VSD).

Cardiac malformations are found in at least 40 percent of patients with Down syndrome[2,3,17]. There is a distinctive spectrum of cardiac defects with an overpresentation of endocardial cushion defects compared with the general population. The most common lesions (in decreasing order of frequency) include common atrioventricular canal, VSD, ASD, tetralogy of Fallot and PDA. Left-sided obstructive lesions such as coarctation and valvar aortic stenosis are rare. Transposition of the great arteries has not been reported[10]. In Turkey, Atalay et al.[15] first described 100 cases with Down syndrome examined by echocardiography. In their report, CHD was detected in 36 percent of these cases (41.7% of these were diagnosed with an endocardial cushion defect and 30.5% with VSD). Tetralogy of Fallot was shown as the most common cyanotic heart disease in the same report. In 1997, the incidence of CHD with Down syndrome was determined as 52.3 percent by Günbey et al.[18]. The most common CHD was endocardial cushion defect (50%). Others were ASD (22.7%), VSD (23.6%), tetralogy of Fallot (5%), bicuspid aortic valve (5%) and tricuspid insufficiency (5%). The incidence of CHD in our study, 71.4 percent, was higher than in others and the most common type of CHD was ASD. Our results in the neonatal period and during childhood were different from those reported by Hoe et al.[8], Atalay et al.[15], Günbey et al.[18] and Normand et al.[19]. This may be due to our small number of cases.

Thyroid dysfunction and infertility are the most significant endocrinologic disorders in patients with Down syndrome[2]. Hypothyroidism occurs in approximately 15 percent of children with Down syndrome prior to adolescence[20]. Studies of thyroid function in children with Down syndrome have shown a prevalence of acquired hypothyroidism that varies widely, from two to 27 percent[21]. In school-aged

children with Down syndrome, hypothyroidism was found in three percent[6]. Fort et al.[22] found an incidence of persistent primary congenital hypothyroidism in infants with Down syndrome about 28 times more than in the general populatilon. In our study, we determined two cases with congenital hypothyroidism (8.3%). The cause of congenital hypothyroidism in infants with Down syndrome remains unknown. It has been assumed that impaired immune surveillance in Down syndrome is a primary mechanism[22].

Five percent of the children with Down syndrome have gastrointestinal abnormalities such as duodenal atresia, Hirschsprung's disease, annular pancreas and anal atresia[23]. The incidence of congenital duodenal obstruction in Down syndrome is 300 times higher than in the general population[3]. Despite the fact that several malformations associated with Down syndrome were seen, we noted only eight reports in the literature, including our own, cholelithiasis in patients with Down syndrome[24-26]. We therefore examined 28 of the cases for cholelithiasis by ultrasonography and found only two infants with cholelithiasis who had a history of polycythemia and hyperbilirubinemia in the neonatal period. In our cases, only three patients (10%) had a history of polycythemia in the neonatal period and two of these (66.6%) had gallstones. History of hyperbilirubinemia in the neonatal period was detected in eight patients. In four of these, jaundice disappeared on phototherapy. One normalized following exchange transfusion, and one case recovered spontaneously. According to studies by Balcı et al.[27] and Bostanoğlu[28] the prevalence of cholelithiasis in 286 Down syndrome patients was 5.2 percent (15 patients).

Annular pancreas is frequently associated with other malformations. Among 52 cases reported by Salzer et al.[29], there were nine children with Down syndrome. This rate is higher than in our study (3.3%). Incidence of gastrointestinal anomaly in our study was 10 percent.

Children with Down syndrome carry an elevated risk of developing clonal hematologic disorders and a 10-fold increased risk of leukemia during the first decade of life[10]. Down syndrome patients have about a one percent risk of developing acute non-lymphoblastic and lymphoblastic leukemia during their lifetimes[30].

Transient myeloproliferative disorder and subsequent acute myeloid leukemia (AML) occur with increased frequency in infants and children with Down syndrome[31]. Transient acute leukemia noted during the first few days of life mimics acute lymphoblastic leukemia (ALL); the hematologic status of these neonates returns to normal in one to four months with only supportive therapy[31-33].

In our study congenital leukemia was determined in one patient and acute lymphoblastic leukemia in another patient. Incidence of leukemia in our study was found as 10 percent.

In view of our findings, it is suggested that children with Down syndrome must be evaluated for cholelithiasis, especially if a history of polycythemia in the neonatal period is present. But the number of our cases was small. We feel that further studies, involving large series, must be evaluated for incidence of cholelithiasis.

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