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NOONAN'S SYNDROME IN ASSOCIATION WITH ACUTE LEUKEMIA

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□ Noonan's syndrome (NS) is a syndrome with multiple congenital anomalies, characterized by craniofacial anomalies, congenital heart disease, skeletal and genital abnormalities, and mild mental retardation. Chromosomal abnormalities have been found in only a few cases. The combination of NS and acute leukemia has been reported in only three cases. Two additional cases are described here.

Keywords acute leukemia, acute lymphatic leukemia, acute myeloid leukemia, Noonan's syndrome

Noonan's syndrome (NS) is a syndrome with multiple congenital anomalies. It is also one of the most common malformation conditions in humans, with an estimated incidence of 1 in 1,000 to 2,500 live births [1, 2]. The syndrome is characterized by craniofacial anomalies, including ptosis, hypertelorism and epicanthus, an anti-mongoloid slant of palpebral fissures, low-set, posteriorly angulated ears, a deeply grooved philtrum with high, wide peaks of the vermilion border of the upper lip, a high arched palate, and micrognathia. In addition to these features the syndrome is often accompanied by congenital heart disease (pulmonary valve stenosis), skeletal abnormalities (short stature and a short, webbed neck and thorax abnormalities), genital malformations, and mild mental retardation [1].

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The expression of NS varies strongly and it may be difficult to recognize in mildly affected individuals. NS also has a changing phenotype with age [2]. These factors can lead to an underestimation of its incidence. Phenotypically this syndrome is associated with Turner's syndrome, but in contrast to the 45,XO chromosomal abnormality in Turner's syndrome, there has seldom been found a chromosomal anomaly in NS patients. An autosomal inheritance of NS has been suggested, but convincing evidence is still lacking [1, 4, 5]. In view of the variability and frequency of NS, genetic heterogeneity must be considered [1].

In the outpatient department we were confronted with two patients with the Noonan phenotype suffering from acute leukemia. A possible association of NS with malignant manifestations has been described in only a few reports. NS has been reported in combination with three cases of acute lymphatic leukemia (ALL) [5, 6], with one case of malignant schwannoma [7], and with one case of acute promyelocytic leukemia and congenital hypoplastic anemia [8]. In this paper we describe two cases of NS associated with acute leukemia.

CASE REPORTS

Case 1

A 9-year-old boy was admitted to the outpatient department of the Academic Hospital Nymegen with complaints of weakness, weight loss, swollen eyelids, and hematomas. He was very pale and splenomegaly was found. Further investigation of his complaints revealed an acute myeloid leukemia (AML). Examination showed a boy too small for his age (less than the 3rd percentile) with an atypical facial expression: a flat, round face, a small jaw, and a partly double toothline. His mother was mentally retarded and a 3-year-old older brother was also too small for age. The phenotypic characteristics and the family history made it plausible that the boy suffered from an underlying inherited syndrome. This was further investigated during the clinical therapy for his AML. No chromosomal abnormalities were found. In cooperation with the Clinical Genetics Department, it was concluded that the boy had NS, despite the absence of cardiac abnormalities. Accompanying features and symptoms of NS were not found in the mother or brother, but a mild affection with different expression could not be excluded. Complete remission of the AML was achieved after chemotherapy (Dutch Childhood Leukemia Study Group, acute nonlymphocytic leukemia [ANLL] 87).

Case 2

A girl born after a full-term pregnancy by cesarean section, because of cephalopelvic disproportion, was kept in the outpatient department of the Academic Medical Center in Amsterdam because of a persisting hepatosplenomegaly, feeding problems, a slow gain in weight and length, and preleukemic blood parameters (hemoglobin 5.8 mmol/L, reticulocytes 43/1,000, total white cell count $40.6 \times 10^9/L$, platelets $137 \times 10^9/L$). She had some typical dysmorphic features, including microcephaly (less than the 3rd percentile), low implantation of the hair, a short, webbed neck, hypertelorism, a small nose, a slight anti-mongoloid slant of the palpebral fissures, a malformed palate, and dysplastic ears with posterior angulation (Figure 1). Her extremities were relatively short. Ultrasound examination of the heart revealed a pulmonary artery stenosis. There was also a partial deficiency of coagulation factor XII (44%). The girl was diagnosed with NS based on the particular phenotype in combination with the pulmonary stenosis and the normal chromosomal pattern. At the age of 10 months she became more pale, and had petechiae and spontaneous mucous membrane bleedings. Laboratory findings showed anemia, thrombocytopenia, and leukocytosis. Bone marrow examination confirmed the diagnosis of ALL with a blast count of 83%. Therapy was started and complete remission was established. On consultation in the outpatient department the girl showed episodes of both increased white blood cells and a low platelet count. Bone marrow aspiration at that time showed no evidence of leukemia. She remains in her first complete remission (3 years 8 months).

DISCUSSION

Noonan's syndrome is associated with several other diseases, including neurofibromatosis type 1 [9, 10], Watson syndrome [10], leopard syndrome [11], and in a single case DiGeorge syndrome [12]. In only three cases has NS-associated ALL been described [5, 6]. The genetic association of these entities and NS has not yet been proven. Wilson et al. [12] found a monosomy 22q11 in a person with both NS and DiGeorge syndrome. It was hypothesized that the genetic source of NA might be found on chromosome 22. Chery et al. [3] reported a balanced reciprocal autosomal translocation between chromosome 3 and chromosome 22, and suggested that chromosome 22 could be a candidate for the localization of NS. This was based on the involvement of this chromosome in



Figure 1. Case 2 at age 4 years. Note the microcephaly, hypertelorism, small nose, and anti-mongoloid slant of the palpebral fissures.

NS and the cardio-facio-cutaneous syndrome, together with the possibility that these syndromes may be one single entity [13].

The three patients with both NS and ALL had a normal karyotype. The incidence of malignant diseases in children with NS is unknown [6]. In our opinion, with reference to our cases and the available literature, it is difficult at the present time to prove or refute predisposition for leukemia in NS. It is known and accepted that in other more obvious and typical syndromes genetic aspects play an important role in the etiology of childhood leukemia. Neurofibromatosis, Down's syndrome, Fanconi's syndrome, Bloom syndrome, and ataxia telangiectasia are obvious identifiable syndromes with a predisposition for leukemic manifestations [14].

The fact that chromosome 22 has been reported to be involved in one case of NS, and in acute leukemia [15] can lead to speculation that there may be a connection between the two related to abnormalities on the chromosome. There have not been any studies on this correlation yet, probably because of the low incidence of the combination of NS and acute leukemia. A thorough examination in cooperation with the clinical genetics department, as well as further evaluation of the parents and siblings seems worthwhile to facilitate the detection and to establish a complete diagnostic result. A study of the occurrence of NS characteristics in new leukemia patients might reveal a higher incidence of this combination.

REFERENCES

1. Mendez HMM, Opitz JM. Noonan syndrome: a review. *Am J Med Genet.* 1985;21:493–506.
2. Allanson JE, Hall JG, Hughes HE, et al. Noonan syndrome: a changing phenotype. *Am J Med Genet.* 1985;21:507–514.
3. Chery M, Philippe C, Worms AM, et al. The Noonan syndrome; the Nancy experience revisited. *Genet Couns.* 1993;4(2):113–118.
4. Sharland M, Patton MA, Talbot S, et al. Coagulation factor deficiencies and abnormal bleeding in Noonan syndrome. *Lancet.* 1992;339:19–21.
5. Piombo M, Rosanda C, Pasino M, et al. Acute lymphoblastic leukemia in Noonan syndrome: report of two cases. *Med Pediatr Oncol.* 1993;21(6):454–455.
6. Attard-Montalto SP, Kingston JE, Eden T. Noonan syndrome and acute lymphoblastic leukaemia. *Med Pediatr Oncol.* 1994;23:391–392. Letter.
7. Kaplan MS, Opitz JM, Gosset FR. Noonan syndrome: a case with elevated serum alkaline phosphatase levels and malignant schwannoma of the left forearm. *Am J Dis Child.* 1968;116:359–366.
8. Krishan EU, Wegner K, Garg SK. Congenital hypoplastic anemia terminating in acute promyelitic leukemia. *Pediatrics.* 1978;61(6):898–901.
9. Allanson JE, Hall JG, Van Allen MI. Noonan phenotype associated with neurofibromatosis. *Am J Med Genet.* 1985;21:457–462.
10. Flinthoff WF, Bahuau M, Lyonnet S, et al. No evidence for linkage to the type 1 or type 2 neurofibromatosis loci in Noonan syndrome families. *Am J Med Genet.* 1993;46(6):700–705.
11. Blieden LC, Schneeweiss A, Shem-Tou A, et al. Unifying link between Noonan's and Leopard's syndromes? *Pediatr Cardiol.* 1983;4:168–169.
12. Wilson DI, Bennet Britton S, McKeown C, et al. Noonan's and DiGeorge syndromes with monosomy 22q11. *Arch Dis Child.* 1993;68:187–189.
13. Reynolds JF, Neri G, Herman JP, et al. New multiple congenital anomalies/mental retardation syndrome with cardio-facio-cutaneous involvement: the CFC-syndrome. *Am J Med Genet.* 1986;25:413–427.
14. Neglia JP, Robinson LL. Epidemiology of the childhood acute leukemias. *Pediatr Clin North Am.* 1988;35(4):675–692.
15. Cannistra SA. Chronic myelogenous leukemia as a model for the genetic basis of cancer. *Hematol Oncol Clin North Am.* 1990;4(2):337–357.