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Features of Neurofibromatosis - Noonan Syndrome Associated with Moyamoya Disease and Tetralogy of Fallot

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SUMMARY

We report a girl with manifestations resembling Noonan syndrome associated with moyamoya disease and tetralogy of Fallot. Other manifestations, included a relatively small head, deeply set eyes with upward slant of palpebral fissures, high nasal bridge, posteriorly angulated low set and large ears, low posterior hair line, broad neck with webbing, sloping shoulders, widely spaced nipples, bilateral transverse palmar creases, cafe-au-lait spots with freckling, solitary neurofibromas, short stature, and mild to borderline mental retardation. High resolution chromosomal analysis was normal. The unusual constellation of manifestations may expand the spectrum of neurofibromatosis-Noonan syndrome or represent a distinct entity.

Introduction

Noonan Syndrome (NS) is a relatively common multiple congenital anomaly syndrome that shows wide phenotypic variability.[1] Neurofibromatosis type 1 (NF 1) is even more common than NS and also shows wide variability of expression. In some families with NF 1, NS phenotype has been occasionally manifested either partially or fully. [2,3,4.] Recent studies suggested that NS phenotype associated with NF 1 is probably the result of variable expression of NF gene on chromosome 17. [5] It has been shown that NS per se is not linked to the NF 1 locus. [6] Here we report an unusual association of NS-like phenotype with NF 1, moyamoya disease and tetralogy of Fallot in a female child with unremarkable family history of any of these conditions.

Case Report

The patient K.B. was evaluated at the age of 16 months because of some Noonan syndrome manifestations and several cafe-au-lait spots. She was born at term by Caesarean section for breech presentation and weighed 2440 g. Pregnancy history was unremarkable. At birth, she was noted to have cyanosis and heart murmur in addition to 2 cafe-au-lait spots. She was diagnosed as having tetralogy of Fallot by cardiac catheterization and subsequently underwent several corrective surgeries. At the age of three months she was noted to have

dysmorphic features and her weight, length and OFC were below the 3rd centile. G-banded peripheral blood chromosomes were normal.

At six months, she had a brief generalized tonic-clonic seizure during caridac catheterization. CT scan of the head and EEG were unremarkable and she received no anticonvulsant medication.

At the age of 16 months, weight was 8.09 kg (3rd percentile), height was 71 cm (3rd percentile) and OFC was 44 cm (3rd percentile). Manifestations included telecanthus, flat nasal bridge, high arched palate with normal dentition and low-set, posteriorly angulated ears. The neck was short and broad with low posterior hair line. Inter-nipple distance was at the 97th percentile. The hands showed mild clubbing of the fingers with bilateral transverse single palmar creases. Also, she was noted to have 5-6 significant cafe-au-lait spots on different parts of the body with no evidence of axillary or inguinal freckling. Ophthalmologic evaluation was normal, and neurologic examination was nonfocal, although she was found to have significant speech and motoric delay. Chest x-rays showed no vertebral anomalies.

At 25 months, she suffered a prolonged left sided focal motor seizure that resulted in acute hemiparesis. EEG and CT scan of the head were normal. Although she was maintained on therapeutic doses of phenobarbital, she developed recurrent seizures within the next month. Cerebral MRI demonstrated ischemic areas in the right hemisphere and cerebral angiography revealed the characteristic findings of moyamoya including bilateral occlusions of both internal carotid arteries, a net-like cluster of small collateral vessels bilaterally in the region of the basal ganglia but good distal branches, and evidence of a vascular process or occlusions. Angiography also demonstrated a unilateral primitive trigeminal artery and dural branch of the internal carotid artery.

At the age of 5-1/2 years, her weight was 17.2 kg (25th percentile), height was 103.3 cm (3rd percentile) and head circumference was

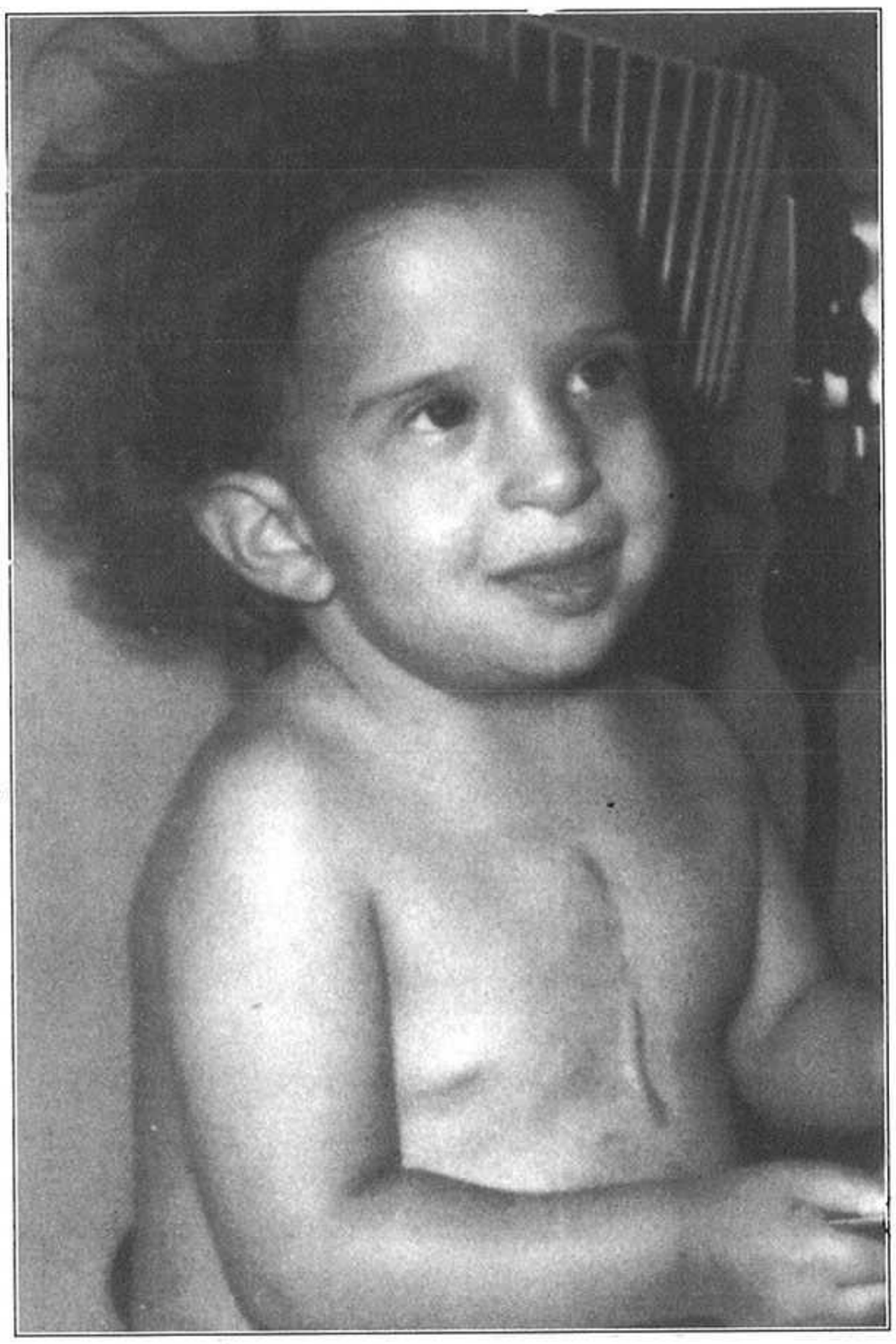

Fig.1:Patient at the age of 25 months.

48.1 cm (3rd percentile). Manifestations (Fig. 1 and Figs. 2 a,b) included deeply set eyes with upward slant of palpebral fissures. Inner canthal distance (ICD) was 3.2 cm (90th percentile). Interpupillary distance (IPD) 5.5 cm (90th percentile) and palpebral fissures 2.4 cm (10th percentile). She showed high nasal bridge, relative micrognathia, low-set posteriorly angulated large ears, broad neck with sloping shoulders, mild neck webbing, and low posterior hairline. There was a midline scar in the chest and the nipples were widely spaced. Hands showed bilateral single transverse palmar creases. Skin examination showed 6-7 significant cafe-au-lait spots on different parts of the body (10 mm in diameter), mild axillary and inguinal freckling, and few fleshy brown-colored superficial

Fig.2a:Patient at the age of 5-1/2 years, full face.

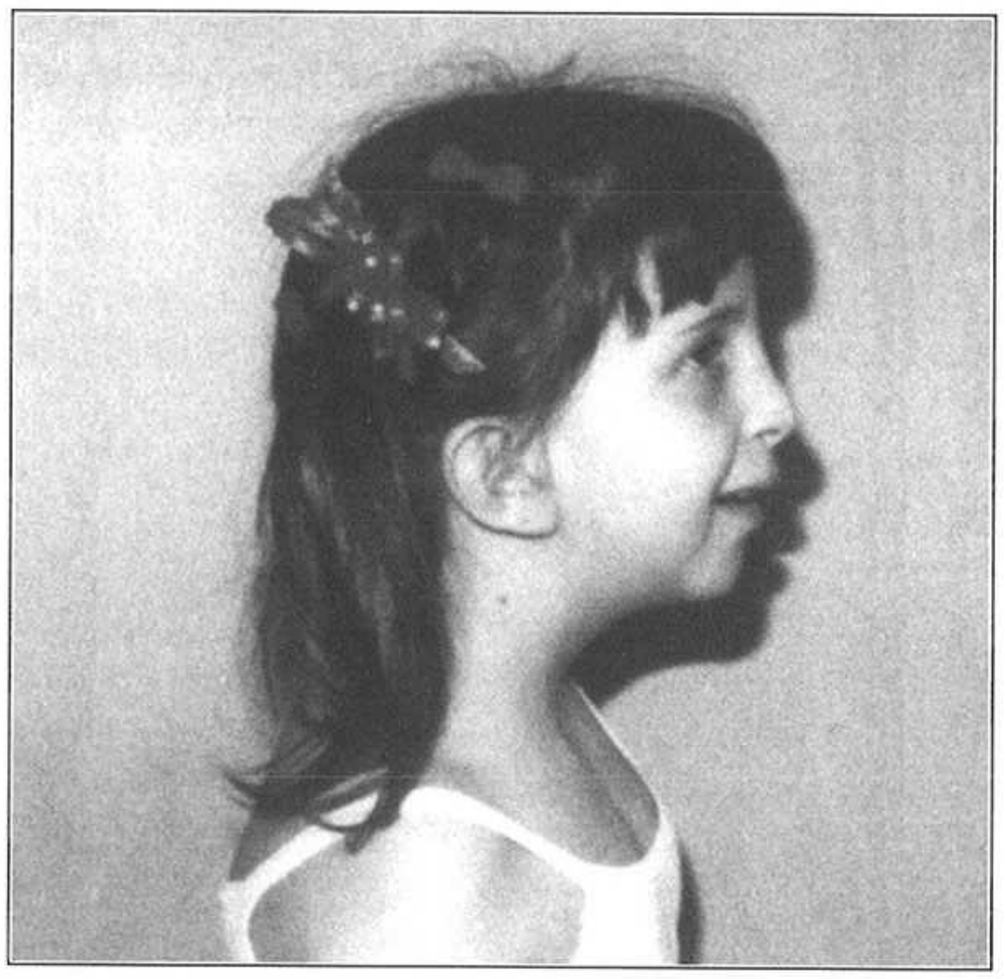

Fig.2b:Patient at the age of 5-1/2 years, profile.

lesions on the abdomen and back (about 2-3 mm each), suggestive of solitary neurofibromas. Developmentally, she was borderline normal. General physical and neurological examination were otherwise unremarkable. High resolution G-banded chromosome analysis from peripheral white blood cell was normal.

Family study showed no similarly affected individuals. There was no one with NF 2, NS, mental retardation, or birth defects. Mother and maternal grandmother were short. Their heights were 152 cm and 150 cm respectively. The family is of Italian and Italian-Irish descent with no consanguinity. Father and mother were 34 and 32 years old respectively, at the time of her birth. They had a 3-1/2 year old normal daughter and history of an early spontaneous abortion.

Discussion

Differential diagnosis must include NS that can be associated with cafe-au-lait spots, and pulmonic stenosis as a "common" heart defect which can be occasionally accompanied by some components of tetralogy of Fallot.[1] However, moyamoya disease has not been a recognized finding in NS. In addition, the facial appearance in the present patient with deeply set eyes, upward-slant of palpebral fissures, and microcephaly is dissimilar.

Also, she differs from clinically related conditions, namely cardiofaciocutaneous (CFC) syndrome,[7] Watson Syndrome, and LEOPARD syndrome, [8,9] and other NS-like syndromes. [10,11,13,14,15,16]

On the other hand, the presence of cafe-au-lait spots in a significant number and size in addition to axillary and inguinal freckling and neurofibromas fulfills the NIH diagnostic criteria of NF 1. [17,18] The presence of moyamoya disease is probably supportive of the diagnosis of NF and does not exclude it, since moyamoya disease is among the recognized manifestations of NF. However, although NS is a well-known association, the phenotype in this girl is quite distinguishable from classical NS. The main differences are: the relatively small head, facial appearance, bilateral single palmar creases and the complexity of the heart defect. The question now is whether this case represents an aspect of NF-NS phenotypic heterogeneity and might extend its spectrum, or is a new syndrome that resembles NF-NS, the genetic etiology of which is unknown. When the mutations at the Noonan and at the NF loci have been

characterized, it may be informative to look at these loci specifically for a mutation.

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References

1.MENDEZ HMM, OPITZ JM. Noonan syndrome: a review. Am J Med Genet 1985; 21:493-506.

2.ALLANSON JE, HALL JG, VAN ALLEN MI. Noonan phenotype with neurofibromatosis. Am J Med Genet 1985; 21:457-462.

3.OPTIZ JM, WEAVER DD. Editorial comment. The Neurofibromatosis-Noonan Syndrome. Am J Med Genet 1985; 21:471-476.

4.ABUELO DN, MERYASH DL. Neurofibromatosis with fully expressed Noonan Syndrome. Am J Med Genet 1988; 29:937-941.

5.STERN HJ, SAAL HM, LEE JS ET AL. Clinical variability of type 1 neurofibromatosis: Is there a neurofibromatosis-Noonan phenotype. J Med Genet 1992; 29:184-187.

6.SHARELAND M, TAYLOR R, PATTON MA ET AL. Absence of linkage of Noonan Syndrome to neurofibromatosis type 1 locus. J Med Genet 1992; 29:188-190.

7.REYNOLDS JF, NERI G, HERRMANN JP ET AL. New multiple congenital anomalies/mental retardation syndrome with cardio-facio-cutaneous involvement. The CFC syndrome. Am J Med Genet 1986; 25:413-417.

80WATSON GH. Pulmonary stenosis cafe-au-lait spots, and dull intelligence. Arch Dis Childh 1967; 42:303-307.

9.SANCHEZ-CASCOS A. Genetics of pulmonic stenosis. Acta Cardiol (Brux) 1972; 27:316-330.

10.KOUSSEFF GB, NICHOLS P. A new autosomal recessive syndrome with Noonan-like phenotype, myopathy with congenital contractures and malignant hyperthermia. Birth Defects (OAS) 1985; 21(2):111-117.

11.BARAISTER M, PATTON MA. A Noonan-like short stature syndrome with sparse hair. J Med Genet 1986; 23:161-164.

12.SANCHEZ-CORONA J, CANTU JM. The Craniocardioskeletal Syndrome and the Noonan-like Short Stature Syndrome are possibly the same entity. J Med Genet 1987; 25:510.

13.BARAISTER M, WINTER RM. Iris coloboma, ptosis, hypertelorism, and mental retardation: a new syndrome. J Med Genet 1988; 25:41-43.

14.HALL BD. Iris coloboma, ptosis, hypertelorism, and mental retardation. J Med Genet 1989; 26:69.

15.SHEPHERD RC, GOUDIE DR, TOLMIE JL. Unknown Syndrome: Noonan-like craniofacial features, digital anomalies and premature birth. J Med Jenet 1989; 26:470-472.

16.COHEN MM, JR., GORLIN RJ. Noonan-like/multiple giant cell lesion syndrome. Am J Med Genet 1991; 40:159-166.

17.RICCARDI VM, EICHNER JE. Neurofibromatosis: phenotype, natural history and pathogenesis. Baltimore: Johns Hopkins University Press, 1986.

18.KORF BR. Diagnosis of neurofibromatosis and clinical overview. In: Neurofibromatosis: A Handbook for patients, families and health care professional. New York: The National Neurofibromatosis Foundation, Inc., Thieme Medical Publishers, Inc., 1990: pp. 15-28.

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