Megalocornea, macrocephaly, mental and motor retardation: MMMM syndrome (Neuhäuser syndrome) in two sisters with hypoplastic corpus callosum

Sevim Balcı[1], Özlem Tekşam[1], Şansal Gedik[2]

Departments of [1]Pediatrics and [2]Ophthalmology, Hacettepe University Faculty of Medicine, Ankara, Turkey

SUMMARY: Balcı S, Tekşam Ö, Gedik Ş. Megalocornea, macrocephaly, mental and motor retardation: MMMM syndrome (Neuhäuser syndrome) in two sisters with hyoplastic corpus callosum. Turk J Pediatr 2002; 44: 274-277.

We report two sisters with Neuhäuser [megalocornea, macrocephaly, mental and motor retardation MMMM] syndrome. They also had hypotonia, incomplete cleft palate, bifid uvula, depressed nasal bridge, epicanthal folds, hypoplastic labia major, micrognathia and pectus excavatum. Their brain magnetic resonance imaging showed cortical atrophy, large fourth ventricle and hypoplasia of corpus callosum. These findings have not been reported before in MMMM syndrome. Prenatal sonography could have been helpful if the mother had asked for genetic counseling given the presence of hypoplasia of corpus callosum and Dandy-Walker variant.

Key words: megalocornea, macrocephaly, mental retardation, hypotomia, Neuhäuser syndrome, posterior cleft palate, hypoplastic corpus callosum, MMMM syndrome.

The association of megalocornea, mental-motor retardation and macrocephaly (MMMM) is a rare autosomal recessive syndrome and a well delineated clinical entity. This syndrome was first described by Neuhäuser et al.[1] in 1975. Later, similar cases with variable expression were reported by Schmidt and Rapin et al.[2], Del Giudice et al.[3], Rass-Rothschild et al.[4], Santolaya et al.[5] and finally Verloes et al.[6]. We describe two sisters with MMMM syndrome or Neuhäuser syndrome who are different from the previously reported cases with findings such as hypoplasia of the corpus callosum. These findings have not been described before and, we believe, they are very important, especially in the differential diagnosis of MMMM syndrome during early prenatal diagnosis.

Case Reports

Case 1

A 10-month-old female patient was admitted to our hospital with chief complaints of mental-motor retardation, hypotonia, megalocornea and incomplete cleft palate. The parents were first-degree relatives. Our patient was the third child of the family. The first male child had died at 15 days, possibly from meconium aspiration. The second child was a nine-year-old healthy male. On physical examination of the patient, head circumference and length were 49 cm (>95th percentile) and 68 cm (10th-25th percentile), respectively. The weight was 6,700 g (<5th percentile). She had motor retardation, hypotonia, depressed nasal bridge, incomplete cleft palate, bifid uvula and micrognathia. Skull and vertebral x-rays, abdominal sonography, chromosome analysis (46, XX), urine and blood amino acid chromatography were normal. TORCH serology was negative. Brain magnetic resonance imaging (MRI) showed large cisterna magna and fourth ventricle. Corpus callosum was hypoplastic. Ophthalmologic examination revealed bilateral megalocornea (corneal diameter: 15 mm). Unfortunately, the patient died in the first year of life.

Case 2 (Sister of Case 1)

Case 2 was a 14-month-old girl who was the fourth child of the family. Unfortunately, the mother did not ask for genetic counseling during the pregnancy. The patient was first admitted to our department when she was 14-months-

old. On physical examination, the weight was 12 kg (95th percentile), and length was 78 cm (75th percentile). The head circumference was 51 cm (>95th percentile) (Fig. 1). She had severe mental-motor retardation, hypotonia, epicanthal folds, depressed nasal bridge, sparse and blonde hair, low-set ears, incomplete cleft palate, bifid uvula, hemangioma on the neck, short columella and philtrum, pectus excavatum, and hypoplastic labia major. Urine and blood amino acid chromatography, chromosome analysis (46 XX), and echocardiogram were normal. Cranial MRI and computed tomography (CT) showed hypoplasia of corpus callosum and cerebellum, large fourth ventricle, frontal-temporal cortical atrophy and Dandy-Walker variant (Fig. 2). Ophthalmologic examination showed megalocornea (diameter: 16 mm). Iris, anterior segment and intraocular pressure were normal.

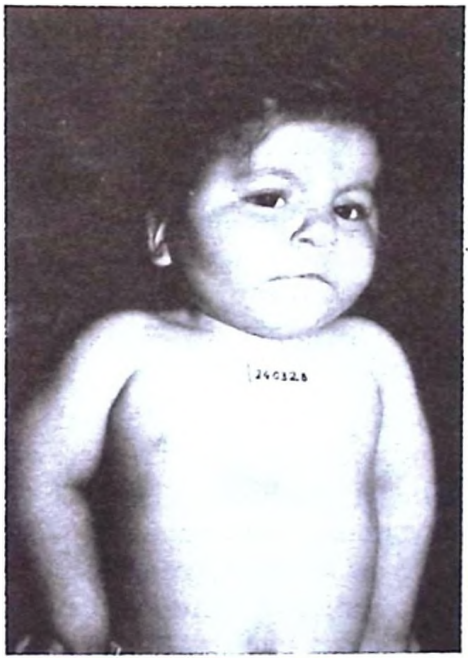

Fig. 1a: The 14-month-old girl (Case 2) with megalocornea, hypotonia, and epicanthal folds.

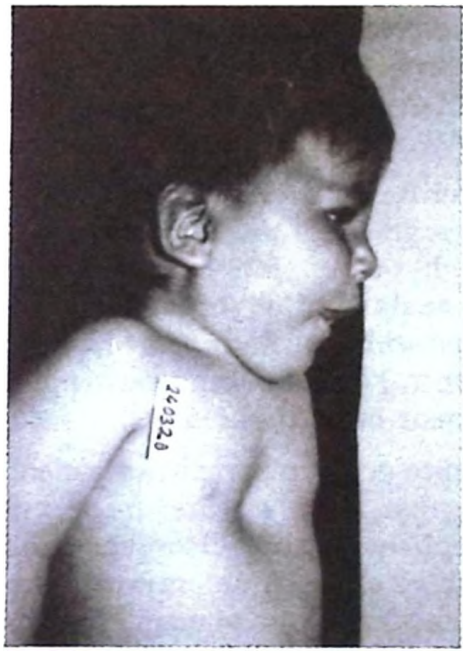

Fig. 1b: Case 2: Note depressed nasal bridge, low-set ears and pectus excavatum.

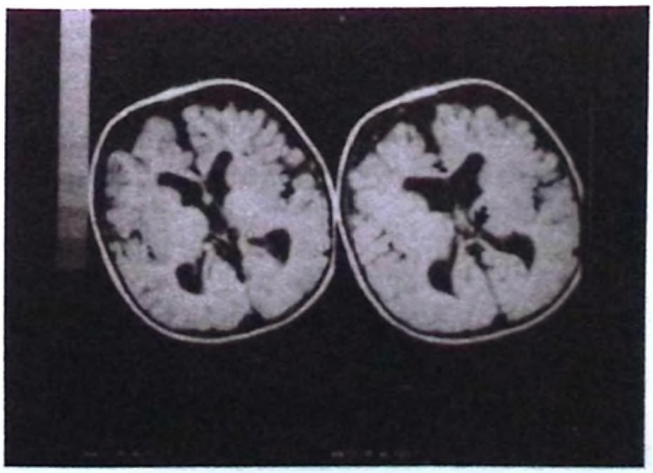

Fig. 2a: Brain magnetic resonance imaging (MRI) of Case 2 dmonstrates cortical atrophy, and hypoplasia of corpus callosum (arrow).

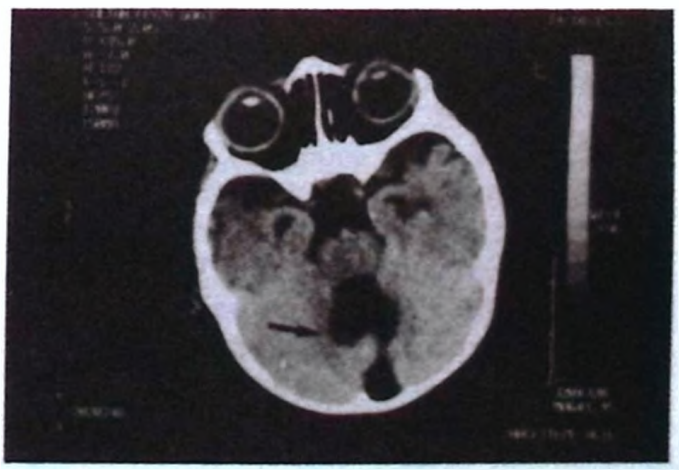

Fig. 2b: Brain computed tomography (CT) demonstrates large fourth ventricle with hypoplasia of vermis indicating Dandy-Walker variant (arrow).

Discussion

Neuhäuser et al.[1] reported an autosomal recessive entity characterized by mental retardation, seizures, muscular hypotonia and megalocornea in 1975. All of their patients (3 siblings and 4 sporadic cases) were moderately to severely retarded and had delayed motor development and megalocornea. Seizures and abnormal EEG recordings were reported in four of seven patients. Santolaya et al.[5] thought that congenital hypotonia might be another major sign of the Neuhäuser syndrome. Santolaya et al.[5] and Raas-Rothschild et al.[4] revealed that mental retardation and megalocornea are nonspecific findings. They suggested that hypotonia is an additional finding in MMMM syndrome.

Megalocornea is a developmental anomaly of the anterior segment of the globe without signs of ocular hypertension[1]. Iris hypoplasia, iridodonesis and myopia are frequently associated with megalocornea. Megalocornea is greater than 12.5 mm of corneal diameter[7], and was present in both our cases.

Del Giudice et al.[3] reported two patients. They thought that short stature, microcephaly or macrocephaly, seizure disorder, neurological symptoms and some minor anomalies represented less common manifestations in this syndrome. They accepted mental retardation and megalocornea as the two sufficient criteria for diagnosis. Frydman et al.[8] described two patients with macrocephaly, mild mental retardation and megalocornea, as well as hypotonia, poor coordination and swallowing difficulties, suggesting that considerable clinical variability or true genetic heterogeneity may be seen in this syndrome. Verloes et al.[6] noticed the heterogeneity in megalocornea, mental-motor retardation (MMR) syndrome and they classified it into five types. Type 1 (Neuhäuser) includes iris hypoplasia, minor anomalies, variable mental retardation and seizures. Type 2 (Frank-Temtamy) is composed of megalocornea, camptodactyly, scoliosis and growth retardation. Type 3 includes normal irides, severe hypotonia, relative or absolute macrocephaly and minor anomalies. Type 4 (Frydman) includes normal irides, megalencephaly and obesity. Type 5 includes unclassifiable cases.

In our two affected sisters, severe mental-motor retardation, megalocornea, hypotonia, incomplete cleft palate, bifid uvula, depressed nasal bridge and micrognathia were present. Incomplete cleft palate can be seen as a minor finding in MMMM syndrome as seen in our cases. Palate abnormalities including high palate[1,3,8], flat palate[1] and low palate with a double convexity and a median groove[6] have been described in previous cases; however, more cases should be described to be able to define cleft palate as a specific finding in MMMM syndrome. Although it is not a specific finding, cleft palate could also be helpful in the prenatal diagnosis of this syndrome.

The significance of our cases was the additional findings of corpus callosum hypoplasia and Dandy-Walker variant (Fig. 2). In the previous reported cases, cranial CT revealed normal[5,6] or mild dilatation of the ventricles without hydrocephalus[8]. Verloes et al.[6] described a case in whom cranial CT demonstrated mild diffuse cortical atrophy. Kimura et al.[9] described a patient with primary hypothyroidism and hypomyelination on brain MRI.

Our cases may be a new recessive type of Neuhäuser syndrome with these additional abnormalities. These findings could be potentially helpful for prenatal diagnosis of this syndrome. The etiology of MMMM syndrome has not yet been described; the inheritance pattern in particular remains unclear. In our second case, prenatal ultrasonography could have been helpful if the mother had asked for genetic counseling, given the presence of hypoplasia of corpus callosum and large fourth ventricle in addition to other anomalies in the previous child. We keep DNA samples of these siblings to determine gene defect for future investigations. Finally, corpus callosum hypoplasia can be an additional finding of MMMM syndrome; however, it is not clear whether or not this association is the result of inheritance by autosomal recessive gene from consanguineous parents. More cases are necessary in order to explain the exact nature of this association.

REFERENCES

1. Neuhäuser G, Kaveggia EG, France TD, Opitz JM. Syndrome of mental retardation, seizures, hypotonic cerebral palsy and megalocornea, recessively inherited. Z Kinderheilk 1975; 120: 1-18.
2. Schmidt R, Rapin L. The syndrome of mental retardation and megalocornea. Am J Hum Genet 1981; 30: 90 A.
3. Del Giudice E, Sartorio R, Romano A, Carrozzo R, Andria G. Megalocornea and mental retardation syndrome: two new cases. Am J Med Genet 1987; 26: 417-420.

4. Raas-Rothschild A, Berkenstadt M, Goodman RM. Megalocornea and mental retardation syndrome. Am J Med Genet 1988; 29: 221-222.

5. Santolaya JM, Grijalbo A, Delgado A, Erdozain G. Additional case of Neuhäuser megalocornea and mental retardation syndrome with congenital hypotonia. Am J Med Genet 1992; 43: 609-611.

6. Verloes A, Journel H, Elmer C, et al. Heterogeneity versus variability in megalocornea-mental retardation (MMR) syndromes: report of new cases and delineation of probable types. Am J Med Genet 1993; 46: 132-137.

7. François J. "Le hérédité en Ophthalmologie". Paris: Masson; 1961: 332.

8. Frydman M, Berkenstadt A, Raas-Rothschild A, Goodman RM. Megalocornea, macrocephaly, mental and motor retardation (MMMM). Clin Genet 1990; 38: 149-154.

9. Kimura M, Kato M, Yoshino K, Ohtani K, Takeshita K. Megalocornea-mental retardation with delayed myelinization. Am J Med Genet 38: 132-133.