NEUHAUSER SYNDROME: A RARE ASSOCIATION OF MEGALOCORNEA AND MENTAL RETARDATION. REVIEW OF THE LITERATURE AND FURTHER PHENOTYPE DELINEATION

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Summary: Neuhauser syndrome: a rare association of megalocornea and mental retardation. review of the literature and further phenotype delineation: Megalocornea can be observed as an isolated abnormality that is inherited by an X-linked mechanism, or it can be associated with other entities. Megalocornea-mental retardation syndrome, also known as Neuhauser syndrome, is a rare autosomal recessive congenital disorder that presents with megalocornea, mental retardation, hypotonia, and facial dysmorphism, among other signs. With the report of this new case, and after an extensive review of the literature, we attempt to delineate the Neuhauser syndrome phenotype.

Key Words: Neuhauser syndrome – Megalocornea – Mental retardation.

INTRODUCTION

Megalocornea-mental retardation (MMR) syndrome (MIM 249310) is a rare autosomal recessive disorder that was first described in 1975 by Neuhauser et al. (19). Most cases are sporadic and the pathogenesis is still unknown. To date, only 39 cases have been reported in the literature. The three main features of MMR syndrome, which are considered the criteria for diagnosis, are primary megalocornea, mental retardation, and hypotonia (23). Primary megalocornea is a congenital, non-progressive, bilateral condition in which the corneal diameter is more than 12 mm in the absence of elevated intraocular pressure (7). Micro/macrocephaly, facial dysmorphism, delayed psychomotor development, retarded growth, primary hypothyroidism, seizures, joint hyperlaxity, and brain malformations can be also associated with MMR syndrome (24). We report a Mexican patient with Neuhauser syndrome (NS) and review all patients reported to date in order to delineate this rare disease.

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CASE REPORT

The patient, a nine-year-old boy, was the first child of non-consanguineous, young and healthy parents and was born at 36 weeks of gestation by cesarian section due to oligohydramnios and maternal pre-eclampsia; the mother had had a previous miscarriage of unknown cause. At birth, the patient weighed 2,125 g and was 49 cm in length. Head and trunk control occurred at 3 and 7 years, respectively. Congenital hypothyroidism was diagnosed early; at the first month, the patient was hospitalized for feeding difficulties and severe hypotonia. Laryngomalacia was also diagnosed at this time, and lower respiratory tract infections occurred repeatedly.

PHYSICAL EXAMINATION

At the physical examination the patient presented weight 12,500 g (-3 percentile), length 104 cm (-3 percentile), and head circumference 45 cm (-3 percentile). Delayed psychomotor development was evident. Dysmorphic findings included microcephaly, a prominent nasal bridge, large and fleshy ears, mild micrognathia, and thenar hypoplasia (Fig. 1). Neurological examination revealed generalized hypotonia, seizures that were difficult to control, and severely delayed psychomotor development (Table I).

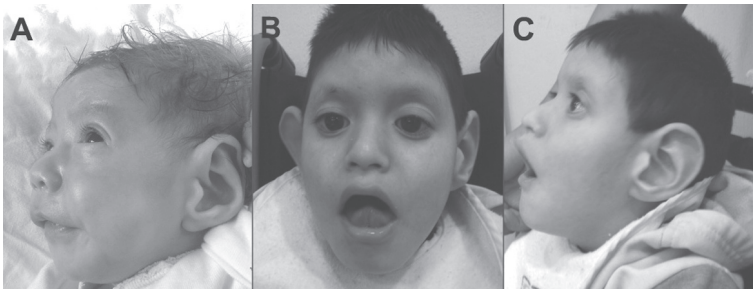

Figure 1: A) Close-up of the patient at two months of age showing megalocornea, hypotonia and large and fleshy ears. B) and C) The patient at nine years of age.

Ophthalmological examination, which took place on four occasions, demonstrated normal irises and normal crystalline and optic disks. Intraocular pressure was repeatedly normal. The last evaluation measured intraocular pressures of 7.1 mmHg in the right eye and 8.5 mmHg in the left eye, and the bilateral corneal diameter was 13.5 mm. Gonioscopy revealed a posterior embryotoxon but no lenticonus. A refractive error (right -7.00 and left -8.00 diopters) was also found.
Echocardiography indicated persistent ductus arteriosus, an atrial septal defect, and anomalous pulmonary venous connection. The patient

had cardiac surgery twice.
Cranial tomography showed normal ventricles, cerebral cortical atrophy, and hypoplasia of the corpus callosum. Abdominal echosonography revealed left hydronephrosis and right renal tubular ectasia. Skeletal X-ray showed decreased bone density. The patient's karyotype was reported to be normal (46, XY).

Table I: Clinical characteristics in 35 patients with Neuhauser syndrome

Characteristics	Published patient*	Present patient	Total	%
Neurological				
Mental retardation	34/34	+	35/35	100
Motor Retardation	34/34	+	35/35	100
EEG abnormal/Seizures	16/26	+	17/27	63
Brain malformation	8/16	+	9/17	53
Dilated ventricles	6/15	-	6/16	38
Ocular				
Megalocornea	34/34	+	35/35	100
Iris hypoplasia	7/19	-	7/20	35
Refractive errors	8/14	+	9/15	60
Craniofacial				
Microcephaly	6/24	+	7/25	28
Macrocephaly	6/24	-	6/25	24
Frontal bossing	20/24	-	20/25	80
Palpebral down slant	8/14	-	8/15	53
Hypertelorism	10/22	-	10/23	44
Broad nasal root	14/17	-	14/18	78
Micrognatia	19/34	+	19/35	54
High arched palate	9/34	-	9/35	26
Osteoarticular				
Joint hyperlaxity	10/34	-	10/35	29
Kyphosis/Scoliosis	9/34	-	9/35	26
Growth retardation	13/27	+	14/28	50
Consanguinity	4/34	-	4/35	11
Primary hypothyroidism	3/10	+	4/11	36
Recurrent infection	7/31	+	8/32	25
Cardiopathy	3/7	+	4/8	50

*References: 1-7, 9-11, 13-15, 17-20, 22-25, 27-29

DISCUSSION

Primary megalocornea is a congenital developmental defect of the eye characterized by non-progressive bilateral enlargement of the corneae with normal intraocular pressure. Primary megalocornea is not associated with other ocular abnormalities and differs from congenital glaucoma or anterior megalophthalmos. Diagnosis of primary megalocornea should be considered in patients with enlarged corneae, normal intraocular pressure, normal iridocorneal angles, an intact Descemet membrane, and no familial history of congenital glaucoma. In congenital glaucoma, elevated intraocular pressure causes eye pain, photophobia, and epiphora and corneal opacification, findings not observed in primary megalocornea (12). In megalophthalmus, both the corneal diameter and the axial length are increased. In most cases, megalocornea is an isolated finding inherited as an X-linked recessive condition (MIM 309300) (16). Megalocornea has also been reported in other conditions or syndromes, most of which include anomalies of the anterior chamber, glaucoma, and secondary megalocornea (9, 29).

The case described in 1973 by Frank et al. (8), with megalocornea, brachycephaly, wide fontanels, a prominent forehead, hypertelorism, prominent eyes, full cheeks, a small chin, bowing of the long bones, and camptodactyly, was first diagnosed as an MMR syndrome. This patient is now known to have Frank-Ter Haar syndrome, a different entity that is caused by homozygous mutations in the TKS4 gene located at 5q35.1 (MIM 249420). For this patient and three other Arab cases described in 1991 by Temtamy et al. (26), the name "Megalocornea-mental retardation-2" (MMR-2) has been suggested.

In 1975, Neuhauser et al. (19) described the association of megalocornea and mental retardation in seven children, including three siblings. In 2008, Opitz et al. (21) proposed that the three familial cases and perhaps some of the sporadic cases reported by Neuhauser et al. represented FG syndrome. We suggest that the sporadic cases, but not the familiar cases, likely had FG syndrome because they do not meet the criteria for megalocornea. Instead, the three familiar cases exhibited megalocornea, mental retardation, hypotonia, seizures, and facial dysmorphisms, completely fulfilling the criteria for NS. Congenital megalocornea is a major criterion that must be present to establish the NS diagnosis.

In 1993, Verloes et al. (29) proposed a tentative classification of MMR based on ocular involvement and other clinical features. This large classification was proposed based on a small number of patients; the authors compared only 21 patients with MMR syndrome and classified the phenotypes into five types. Although 39 patients with NS have

been reported to date, the classification by Verloes et al. (29) does not seem to be applicable. In addition, the cases of Temtamy et al. (26) (Type 2 classification) have now been classified as harboring another syndrome. Our extensive literature review revealed 39 patients reported as having NS. The most important characteristics of these patients are described in Table I.

The male:female ratio of 15:16 indicates no sex bias. Consanguinity was reported in four cases (11%) (6, 17, 28, 29), reinforcing the pattern of autosomal recessive inheritance. Primary megalocornea and mental and motor retardation were present in 100% of patients. The most frequent characteristics (present in more than 50% of the patients) were hypotonia, growth retardation, abnormal electroencephalography/seizures, micro/macrocephaly, brain malformations (cerebral cortical atrophy and hypoplastic corpus callosum), craniofacial abnormalities, cardiopathy, osteoarticular abnormality, and refractive errors. Additional features found at low frequency (and thus not appearing in Table I) in patients with NS include primary hypothyroidism (13, 24), recurrent infections (5, 7, 15, 24, 28, 29), feeding difficulties (4, 7, 9, 29), cerebral hypomyelination (4, 5, 14, 18), dyslipidemia (14, 24, 27), sensorineural deafness (15, 17, 27), laryngomalacia (7, 29), large, fleshy, and cup-shaped ears (6, 9, 28), cardiopathy (7, 28), obesity (6, 9), and cryptorchidism (28, 29).

In 1990, Frydman et al. (9) reported two unrelated patients with megalocornea, macrocephaly and mild mental retardation proposed the term "Megalocornea, macrocephaly, mental and motor retardation syndrome" (MMMM). In this review, we found normal head circumference in 50% of NS cases, microcephaly in 28% of cases, and macrocephaly in 24% of cases, suggesting that macrocephaly is a common feature in NS and does not constitute a different entity.

Del Giudice et al. (6) proposed that mental retardation and megalocornea are two minimal criteria for diagnosis of NS. However, mental and motor retardation are variable features, and several cases show only mild or moderate retardation, or it is not clear in other cases, who can therefore be diagnosed as having an isolated form of megalocornea. In these circumstances, minor criteria should be considered in order to confirm an NS diagnosis or to make an accurate diagnosis.

From this review, we propose that the diagnosis of NS should be made in the presence of mental retardation and megalocornea in the absence of elevated intraocular pressure, with at least one minor feature such as hypotonia, growth retardation, seizures/abnormal electroencephalography, micro/macrocephaly, brain malformations, craniofacial abnormalities, cardiopathy, osteoarticular abnormality, or refractive errors.

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