Jpn J Human Genet 42, 461-465, 1997

Case Report

MEGALOCORNEA-MENTAL RETARDATION SYNDROME: AN ADDITIONAL CASE REPORT

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Summary We report here on a Japanese male infant with megalocornea-mental retardation (MMR) syndrome. He had megalocornea (corneal diameter: 13 mm) without glaucoma, developmental retardation, hypotonia, frontal bossing, high-arched palate, carp-like mouth, micrognathia, and delayed myelination. He seems to be included in Verloes type of the MMR syndrome.

Key Words megalocornea-mental retardation syndrome, MMR syndrome, MCA/MR syndrome

INTRODUCTION

Megalocornea is defined as a developmental anomaly of the anterior segment of the globe, and characterized by nonprogressive and symmetrical enlargement of the cornea without a sign of glaucoma. Megalocornea is suspected in children when corneal diameter is greater than 12.5 mm (Neuhäuser *et al.*, 1975) or 13 mm in adult (12.5 mm in infant) (Verloes *et al.*, 1993). In addition, the anterior chamber is always unusually deep, not shallow as in secondary large cornea seen in glaucoma.

Isolated megalocornea is usually inherited as an X-linked recessive manner (MIM *309300). In the megalocornea-mental retardation (MMR) syndrome, megalocornea is associated with mental retardation, hypotonia and minor anomalies. So far, since first description of the MMR syndrome (Neuhäuser *et al.*, 1975), about 23 cases have been reported (Frank *et al.*, 1973; Schmidt and Rapin, 1981; Del Guidice *et al.*, 1987; Grønbech-Jensen, 1989; Frydman *et al.*, 1990; Kimura *et al.*, 1991; Temtamy *et al.*, 1991; Santolaya *et al.*, 1992; Verloes *et al.*, 1993; Antiñolo *et al.*, 1994). A subclassification of the MMR syndrome due to presumed

Received May 15, 1997; Revised version accepted July 1, 1997.
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genetic heterogeneity has been proposed (Verloes *et al.*, 1993). We report here on an additional case of Japanese boy with the MMR syndrome.

PATIENT

The propositus is an 8-month-old Japanese boy born as the second child to the parents when the father was 36 and the mother was 46 years of age. They denied consanguinity, however, possibility of a distant relationship was suspected in the pedigree. His elder sister was born by cesarean section and is healthy. The pregnancy was uneventful. He was delivered at term by cesarean section. His birthlength was 45 cm (−2.6 SD), birthweight 2,740 g (−1.2 SD), and birth OFC 32 cm (−1.1 SD). He was referred to us at 8 months of age because of mild developmental retardation and minor anomalies. His length was 70.3 cm (±0 SD), weight 7,070 g (−1.9 SD), OFC 43.0 cm (−1.3 SD). He was mildly hypotonic. His craniofacial anomalies were mild plagiocephaly, frontal bossing with mild frontal hirsutism, large eyes, epicanthal folds, strabismus, and grayish blue sclera. Other craniofacial findings included high and broad nasal bridge, short nose, high-arched palate, micrognathia, prominent left ear, prominent antihelices, short philtrum, and carp-like large mouth with long upper lip (Fig. 1). He had small hands and feet, brachyclinodactyly of 5th fingers, tapered long fingers, prominent fingertip pads, cubitus valgus, and a sacral dimple. Ophthalmological examination

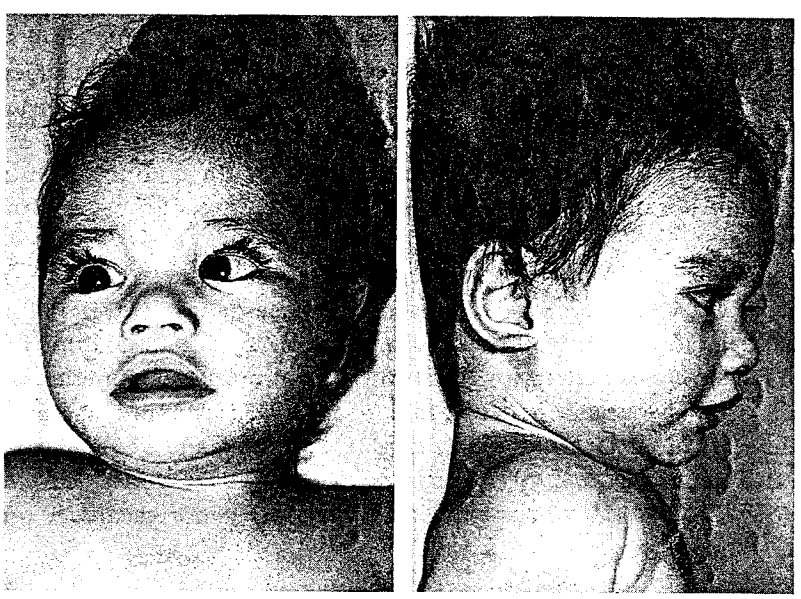

Fig. 1. Facial appearance of the patient. Note megalocornea, prominent forehead, epicanthal folds, high nasal bridge, short nose and carp-like mouth.

revealed megalocornea (corneal diameter: 13 mm) with normal intraorbital pressure and deep anterior chamber, normal irides, and normal fundus. An MRI showed delayed myelination. And a bone survey showed short mesophalanges of the 5th fingers, and advanced bone age (16 months at 8 months of age). His karyotype was normal. Routine laboratory and thyroid function tests were normal. His DQ was 63 at age 8 months.

He was followed up at every 3 months by us. His length was 89.0 cm (−1.2 SD), weight 11.61 kg (−1.4 SD), OFC 48.0 cm (−0.9 SD) at 3 years of age. His development was very slow. He could not walk alone, spoke only one word, and was hyperactive. His DQ was 33.

DISCUSSION

Several well-known malformation syndromes share megalocornea and mental retardation as a part of its clinical findings. However, in most of them, megalocornea is not a cardinal but an occasional finding, and is frequently secondary to glaucoma. Other syndromes do not fit to the present patients except for MMR syndrome (MIM *249310).

Since the original report (Neuhäuser *et al.*, 1975), 24 cases of the MMR syndrome have been reported including the present case (Frank *et al.*, 1973; Schmidt and Rapin, 1981; Del Guidice *et al.*, 1987; Grønbech-Jensen, 1989; Frydman *et al.*, 1990; Kimura *et al.*, 1991; Temtamy *et al.*, 1991; Santolaya *et al.*, 1992; Verloes *et al.*, 1993; Antiñolo *et al.*, 1994). Frequency of the clinical findings seen in these cases are summarized (Table 1). The cardinal findings of the MMR syndrome are mental or developmental retardation, megalocornea, hypotonia, prominent forehead, micrognathia, prominent nasal bridge and thin upperlip or carp-like mouth. All of these are nonspecific and frequently observed in other syndromes. This is the reason why it is questionable whether the MMR syndrome is a specific MCA/MR syndrome or not, and why Raas-Rothschild *et al.* (1988) and Verloes *et al.* (1993) proposed a provisional clinically oriented classification of the MMR syndrome.

Verloes *et al.* (1993) compared phenotypes of 21 cases with the MMR syndrome, and subclassified it into five subtypes. Namely, (1) Neuhäuser type (type 1): autosomal recessive with iris hypoplasia (complicated megalocornea), variable mental retardation, seizures, hypotonia, and minor anomalies (prominent forehead, high nasal bridge, epicanthal folds, micrognathia). (2) Frank-Temtamy type (type 2): autosomal recessive with camptodactyly, (kypho)scoliosis, and growth retardation. (3) Verloes type (type 3): possibly autosomal recessive with normal irides (uncomplicated megalocornea), normal to large OFC, and minor anomalies (frontal bossing, broad prominent nasal root, downslanting, malar hypoplasia, micrognathia, slender thorax, long thin fingers). (4) A possible Frydman type (type 4): associated with large head or true megalencephaly (OFC>3 SD), obesity, and

Table 1. Clinical findings in 24 cases of MMR syndrome.

Findings	No.	(%)
Male : female	14 : 10	
Mental retardation/developmental retardation	24	(100)
Megalocornea	24	(100)
Hypotonia	21	(88)
Prominent forehead	20	(83)
Micrognathia	17	(71)
Prominent nasal bridge	13	(54)
Thin upper lip/carp-like mouth	13	(54)

*11 cases (46%): Growth retardation, seizures/abnormal EEG, epicanthus
*9 cases (38%): High-arched palate, malformed ears
*7 cases (29%): Joint hyperlaxity, microcephaly, downslant, iris hypoplasia
*6 cases (25%): Macrocephaly, dolichocephaly, bulging eyes
*5 cases (21%): Ataxia, hyperactivity, telecanthus/hypertelorism, long thin finger, abnormal knee joints, pes planus, kyphoscoliosis, susceptibility to infections
*Less than 20%: Gingival hyperplasia (17%), short philtrum (17%), small mouth (17%), myopia (17%), iridodonesis (17%), strabismus (17%), brachycephaly (13%), large fontanel (13%), triangular face (13%), thin sparse hair (13%), nystagmus (13%), pectus excavatum (13%), cryptorchidism (13%), sacral dimple (13%), delayed myelination (13%), spastic diplegia (8%), obesity (8%), round face (8%), frontal hirsutism (8%), coarse hair (8%), malar hypoplasia (8%), renal defect (minor) (8%), cafe-au-lait spot (8%), clubfoot (4%)

fleshy ears. (5) Lastly unclassified forms.

According to Verloes' classification (1993), because no iris defects, camptodactyly, magalencephaly or obesity were observed and distant relationship was suspected in the pedigree, our patient seems to fall into Verloes type. However, facial features are different from those of Verloes type. In addition, if presence of iris hypoplasia may be reflected by variability of expression, facial features of our patient is rather similar to Neuhäuser type.

Thus, although it is questionable whether Neuhäuser and Verloes types or other subtypes of the MMR syndrome are causally different, the further clinical and molecular analyses of the MMR syndrome will delineate this syndrome.

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