Short Stature, Myopia, Severe Developmental Delay, and Peculiar Facial Appearance in Two Brothers: A New Syndrome?

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We report on 2 brothers with short stature, microcephaly, myopia, retarded osseous maturation, severe developmental delay, and minor anomalies including temporal narrowing, periorbital fullness, full cheeks in infancy, and protruding lower lip. Both brothers and their parents had normal chromosomes. Fluorescence in situ hybridization with probes from all (sub-)telomeric chromosomal regions excluded a structural rearrangement involving telomeric segments. Because the pattern of congenital abnormalities is not like that of any well-known multiple congenital anomaly/mental retardation syndrome, we suggest a previously undescribed syndrome of autosomal recessive or X-linked inheritance. Am. J. Med. Genet. 86:486–491, 1999.

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INTRODUCTION

A search in POSSUM 5.0 [Possum, 1998] yielded 37 autosomal recessive and 11 X-linked syndromes all characterized by short stature, retarded bone age, and severe developmental delay. Few also comprise with myopia (4 and 1, respectively), and no syndrome fits the pattern of microcephaly, narrow forehead, wide mouth, full lower lip, and slender hands and fingers observed in two brothers of non-consanguineous parents of Ashkenazi Jewish origin recently referred to our institute.

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Fig. 1. a,b: Patient 1 at age 2 years. Note frontal narrowing, inner epicanthic folds, large eyes, convergent squint, full cheeks, and a broad, flat nose.
c,d: Patient 1 at age 9 years 3 months: Note wide mouth, prominent lips, convergent squint, and periorbital fullness.

Squint, narrow forehead, periorbital fullness, inner epicanthic folds, wide mouth, full lower lip, slender hands and fingers, and hypoplastic nails were noted. Inner canthal distance (ICD) (2.2 cm) and interpupillary distance (IPD) (4.3 cm) were below the 3rd centile corresponding to the OFC. Palmar dermatoglyphics were normal. Length of hands (13 cm) and middle fingers (5.2 cm) were below the 3rd centile. In addition, mus-
cular hypotonia and slight contractures of the knees were noted. In contrast to the first evaluation, the face had become longer and cheeks were less full.

A developmental delay was obvious in infancy and increased with age. During the first years of life developmental quotients on language, cognitive and social abilities of approximately 50 were noted; at school age they decreased to 30. Gross and fine motor development were less impaired than cognition and language. Unsupported sitting was achieved at 9 months and walking without support at 23 months. However, there was also a progressive delay of motor competence with increasing age. General hypotonia was present during the first years of life. By school age, active muscle tone had considerably increased.

Patient 2

The boy was born 16 months after his brother. The pregnancy was uneventful. After 42 weeks of gestation weight was 3010 g (10th centile) and length was 46 cm (<10th centile). OFC was not measured. The boy had feeding problems in infancy.

The patient was referred for genetic evaluation at 1½ years of age (Fig. 2 a,b). Initial physical examination showed weight (8.0 kg) and length (70.5 cm) below the 3rd centile, OFC (44.8 cm) on 3rd centile, frontal narrowing, periorbital fullness, inner epicanthic folds, convergent squint, broad nasal bridge, full cheeks, prominent lips, and an open mouth appearance. The karyotype was normal (46,XY).

At a reevaluation at 3 years 5 months, weight (10.9 kg), height (86.4 cm), and OFC (47.0 cm) were below the 3rd centile. Radiographs of the hand revealed a bone age of 2.3 years [Greulich and Pyle, 1959]. The boy had abundant salivation, severe myopia of approximately 12 diopters, convergent squint, and astigmatism. Findings at fundoscopy were unremarkable.

Magnetic resonance imaging of the brain was normal. Findings at endocrinological (T4, TSH, IGFl), metabolic (calcium, phosphorus, transaminases, creatinine), and hematological investigations gave normal results.

At the last examination the boy was 7½ years (Fig. 2 c,d). Weight (17.9 kg), height (114 cm), and OFC (48.5 cm) were still below the 3rd centile. The corresponding SD scores of weight, height and head circumference were -2.4, -3.0, and -3.2, respectively (target height based on parental height: +1.2 to -1.8 SD). The following anomalies were noted: narrow forehead, periorbital fullness, slender hands and feet, and hypoplastic nails. ICD (2.4 cm) and IPD (4.8 cm) were also below the 3rd centile. Similar to his brother, the shape of his face became longer with age. Palmar dermatoglyphics were normal. Length of hands (12.5 cm) and middle fingers (5.0 cm) were below the 3rd centile according to other measurements. In addition, muscular hypotonia and slight contractures of the knees were present.

Similar to his brother, psychomotor development was increasingly delayed with age. Early cognitive and language abilities corresponded to a developmental quotient of approximately 50. By school age the developmental quotient decreased to 30-40. Again, early motor development was less affected than language and cognition. The boy sat unsupported at 10 months and walked alone at 18-20 months. His muscle tone was initially low and increased with age. At that time, the parents reported stereotypic mouth and hand movements and hyperactivity with a short concentration span. General disposition was happy.

Figure 3 and Table I show the growth curves and anthropometric data of both patients.

LABORATORY INVESTIGATIONS AND RESULTS

Routine chromosome analysis was performed in both boys and their parents. QFQ- and GTG-banded metaphases at a level of 400 bands revealed no structural aberration. As part of a large, ongoing study for (sub-) telomeric rearrangements fluorescence in situ hybridization with (sub-) telomeric probes from all human telomeres was performed. The cosmids, P1, and PAC telomere-specific clones were obtained from MRC (Medical Research Council, Oxford, UK) and ATCC (Rockville, MD). Purified DNA from clones was labeled with either biotin-16-dUTP (Boehringer Mannheim, Indianapolis, IN) or digoxigenin-11-dUTP (Boehringer Mannheim) by nick translation. FITC avidin and rhodamine antidigoxigenin were used to detect biotin- and digoxigenin-labeled probes, respectively. Analysis was performed using a Zeiss Axioplan epifluorescence microscope, and images were recorded by a Photometrics CCD KAF1400 camera (Photometrics, Tucson, AZ), controlled with Smart Capture imaging software (Vysis, Inc., Downers Grove, IL). In both boys two normal signals—one on each homologue—were present for all autosomal subtelomeric regions except for those of the short arms of acrocentrics. Furthermore, molecular investigations with one microsatellite marker (ELN) and one restriction length polymorphism (MvaI), both located within the Elastin gene, excluded a deletion of these markers and thus made Williams-Beuren syndrome (WBS) extremely unlikely. Because WBS without a deletion has been described very rarely, it is not possible to definitely rule out this diagnosis.

DISCUSSION

We report on 2 brothers with short stature, myopia, retarded bone age, severe developmental delay, and a peculiar facial gestalt characterized by temporal narrowing, full cheeks in early childhood, wide mouth, and protruding lower lips.

In early childhood, Williams-Beuren syndrome (MIM 190450) [Wu et al., 1998] was suspected, particularly on the basis of developmental delay, friendly behavior, and the facial anomalies of periorbital fullness, blue eyes with a stellate iris pattern, full cheeks, and protruding lower lip. Molecular investigations made this diagnosis very unlikely, but definitive exclusion is not possible. In addition, occurrence in sibs without affected parents, lack of cardiovascular defects, and the change of behavior with time are arguments against this diagnosis.
Fig. 2. a,b: Patient 2 at age 1 year 6 months: Note periorbital fullness, epicanthic folds, convergent squint, and broad nasal bridge. c,d: Patient 2 at 7 years and 11 months: Note epicanthic folds, convergent squint, protruding lips, and wide mouth.

Further differential diagnosis included Coffin-Lowry syndrome (MIM 303600) [Couillault et al., 1988], Kaufman oculo-cerebro-facial syndrome (MIM 244450) [Briscioli et al., 1995; Kaufman et al., 1971], Smith-Fineman-Myers syndrome (MIM 309580) [Adès et al., 1991; Smith et al., 1980], and a single case report of short stature, mental retardation, and eye abnormalities (iris hypoplasia, nuclear cataracts, severe myopia) (MIM 223540) [Mollica et al., 1972].

Compared to our patients, the latter syndrome showed more severe eye abnormalities and no dysmorphisms were mentioned. The pattern of abnormalities described in Kaufman oculo-cerebro-facial syndrome fits with the findings in our patients in many details.
However, myopia in both boys and the findings of upslanting palpebral fissures, telecanthus, thin lips, and skeletal anomalies in Kaufman oculo-cerebro-facial syndrome are arguments against this condition. Smith-Fineman-Myers syndrome differs from the absence of severe myopia and delayed osseous maturation as well as from the typical findings of hypertelorism, microgenia, clubbed fingers, and seizures. Finally, Coffin-Lowry syndrome must be considered. A longish face, protruding lower lips, and developmental delay are consistent with this X-chromosomally inherited syndrome. However, additional anomalies characteristic for Coffin-Lowry syndrome such as downslanting palpebral fissures, broad nasal root with telecanthus, lax joints, and tapering fingers with drumstick terminal phalanges were not noted in our patients. Therefore, we also disregarded this differential diagnosis and refrained from molecular investigations.

Severe myopia, short stature, and slight contrac- tures are also signs towards a collagenopathy. Ho- wever, facial anomalies, retarded bone age, and particularly developmental delay are not typical findings in this heterogeneous group of disorders.

Pedigree analysis did not give a clear evidence for a specific mode of inheritance. A structural chromosomal aberration of the (sub-)telomeric regions was excluded. However, at the present time it is not possible to exclude a small, familiar submicroscopic rearrangement not involving subtelomeric regions. Two affected brothers and three healthy sisters are a hint toward X-chromosomal inheritance. However, the mother did not show any signs of a carrier status and her three brothers are healthy. Both parents were of Ashkenazi Jewish origin and both grandfathers came from Poland. Thus, autosomal recessive inheritance seems more likely, but X-chromosomal inheritance is not excluded. Both should be considered in genetic counselling. Further observations might answer this important question. Because at birth all measurements were within normal ranges or only slightly below and because no malformation was present, currently there is no possibility for any prenatal diagnosis.

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REFERENCES


