Clinical Report

Syndrome of Congenital Cataracts, Sensorineural Deafness, Down Syndrome-like Facial Appearance, Short Stature, and Mental Retardation: Two Additional Cases

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An apparently new syndrome of congenital cataracts, sensorineural deafness, Down syndrome-like facial appearance, short stature, and mental retardation was described by Gripp et al. [1996]. The authors reported on two unrelated patients with congenital cataracts, sensorineural deafness, distinctive facial appearance, mental retardation, postnatal short stature, and skeletal changes. We report on two additional patients with findings most similar to the reported patients by Gripp et al. [1996], including bilateral congenital cataracts, hearing loss, craniofacial abnormalities, short stature, skeletal abnormalities, and developmental delay. Both of the patients reported herein had chromosome microarray analysis, which showed normal results in Patient 2 but abnormal results in Patient 1 and his mother who both had a chromosome 11q25 subtelomere deletion. Patient 1 and his mother’s findings are atypical for the common findings reported in Jacobsen syndrome (11q terminal deletion syndrome), and consistent with the patients reported by Gripp et al. [1996]. The etiology for these cases has been unknown. The microarray results on Patient 1 suggest that the other patients with findings of developmental delay, short stature, congenital cataracts, sensorineural hearing loss, and similar craniofacial features may have either a microdeletion of chromosome 11q terminal region or haploinsufficiency of a gene localized to this region.

Key words: cataracts; sensorineural deafness; Down syndrome-like facial appearance; MCA-MR syndrome; chromosome 11q25 deletion


INTRODUCTION

An “Apparently new syndrome of congenital cataracts, sensorineural deafness, Down syndrome-like facial appearance, short stature, and mental retardation” was described by Gripp et al. [1996]. Ayme and Philip suggested that these patients had similar findings to the patients reported by themselves and other authors [Fine and Lubinsky, 1983; Preus et al., 1984; Suthers et al., 1993; Ayme and Philip, 1996]. They proposed describing this syndrome as the Fine-Lubinsky syndrome. However, later review of these referenced cases concluded that the patients originally reported by Gripp et al. [1996] likely did not have Fine-Lubinsky syndrome [Gripp et al., 1997]. We report on two patients with findings including bilateral congenital cataracts, hearing loss, craniofacial abnormalities, short stature, skeletal abnormalities, and developmental delay who, based upon our review of the preceding cases, are most similar to the patients reported by Gripp et al. [1996]. One of these patients was found to have a chromosome 11q25 deletion.

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subtelomere deletion, which was also identified in his mother. Patient 1 and his mother’s findings are atypical for the common manifestations reported in 11q terminal deletion syndrome (Jacobsen syndrome), and consistent with the patients reported by Gripp et al. [1996]. These results suggest that other patients, including those reported by Gripp et al. [1996], with findings of developmental delay, short stature, congenital cataracts, sensorineural hearing loss, and similar craniofacial features may have either a microdeletion of chromosome 11q terminal region or haploinsufficiency of a gene localized to this region.

**CLINICAL REPORTS**

**Patient 1**

Patient 1 was a 2,480 gram male infant born at 35 weeks gestation by Cesarean secondary to breech presentation to a 23-year-old G1P1 mother and 32-year-old father. His parents were healthy, non-consanguineous, and both with mild mental retardation. He was their only offspring. Family history was negative for history of mental retardation in other family members, cataracts, or hearing loss. Prenatal history was complicated by maternal anxiety and hallucinations treated with Zoloft. There was no reported alcohol or drug use. His mother was rubella immune. The Apgar scores were 2 and 7 at 1 and 5 minutes, respectively. In neonatal period, he was noted to have hypotonia, macrocephaly, epicanthal folds, flattened nasal bridge, and bilateral anterior polar cataracts. Chromosome analysis was 46,XY. Echocardiogram revealed a patent ductus arteriosus. Head ultrasound showed mild ventriculomegaly.

At 2 months of age, on auditory brainstem evoked response (ABR), he had bilateral hearing loss. MRI scan of the brain showed ventricular prominence and prominent cavum vergae. Skeletal survey revealed only 13 sets of ribs. Fluorescence in situ hybridization (FISH) analysis for 22q was normal. Renal ultrasound was normal. Patient 1 was noted to have hypotonia and mild developmental delays. Ophthalmology exam revealed 2.0 mm bilateral anterior polar cataracts with mild hyperopia and normal dilated fundus exam. Surgery was not recommended at the time. On two repeated hearing evaluations, there was severe low frequency loss. On physical examination, length 56 cm (10th centile), weight 16.4 kg (25–50th centile), OFC 50 cm (90th centile), and abnormal findings including: anterior fontanelle 5X5 cm; biparietal frontal bossing; bilateral epicanthal folds; bilateral cataracts; low-set ear positioning; posterior rotation of ears; dimple in left earlobe; flat nasal bridge; short appearing palate, tented upper lip with prominent appearing alveolus, teeth present; and generalized hypotonia (Fig. 3).

At 5 years of age, Patient 1 had bilateral hearing loss requiring hearing aides. His cataracts had not progressed or required surgical removal. He had a history of recurrent episodes of otitis media with PE tube placement. He was described as having a monotone, nasal quality to his voice. His development continued to be delayed: he said ~five single words, but used several signs and a communication board; he was toilet trained, could throw a ball, dressed himself, and knew his colors. His gross and fine motor skills were only slightly behind his chronological age, and he had no behavioral problems. On physical examination at 5 years, the growth parameters indicated his height at 104 cm (10–25th centile), weight 16.4 kg (25–50th centile), OFC 54.5 cm (>95th centile–50th centile for a 5-year-old); and other findings included bilateral epicanthal folds, OC 75 mm, IC 28 mm, PF 22 mm; low set ears with bilateral length 45 mm, high-arched palate; single palmar crease on right with redundant creases on palms and soles of feet; 1 café-au-lait macule on his left knee; no limb bowing or shortening noted. A CBC with differential was normal with platelet count of 328 × 10^9/µl (normal 150–375).

Molecular microarray procedures utilizing genomic DNA extracted from peripheral blood and hybridized with normal reference DNA to SpectralChip 2600 (1MB) was performed on both Patient 1 and his mother. Two clones at 11q25 (RP11-27H17 and RP11-469N6) showed copy number loss by microarray. Based upon coverage of this 1 Mb array, this deletion is 1.0–1.9 Mb in size. FISH studies were performed on metaphase cells from a 72 hr culture utilizing ToTel #11 DNA probe which is specific for the 11p and 11q subtelomere regions. These molecular cytogenetic studies were positive for a deletion of the 11q25 subtelomere region and...
consistent with the abnormal microarray analysis in both Patient 1 and his mother.

**Patient 2**

Patient 2 is the only daughter of healthy, non-consanguineous parents, who subsequently had 1 miscarriage at 12 weeks' gestation. Family history was negative for history of mental retardation in other family members, cataracts, or hearing loss. Her mother's prenatal history was without complications. She was a 3,000 gram infant born at 39 weeks' gestation by Cesarean section to possible placental abruption to a 26-year-old G1P1 woman. In the neonatal period, she failed her newborn hearing screen. Repeat hearing testing with ABRs at 1 month of age revealed severe to profound sensorineural hearing loss.

Bilateral cataracts were diagnosed at approximately at 3½–4 months of age, when her parents noted that her left pupil was grey. She had subsequent removal of the cataracts at 4 months of age (on the left) and at 7 months of age (on the right). On ophthalmology exam, she was noted to have "optic nerve pallor". CT scan of the brain showed some prominence of the ventricular system, but no other brain malformations.

Physical examination at at 5½ months of age showed a length of 62.0 cm (10–25 centile), weight 6.2 kg (10–25 centile), and OFC 42.5 cm (50–75 centile). Her anterior fontanelle was large measuring 6 x 8 cm. There was mild frontal bossing, bilateral epicanthal folds, strabismus, short nasal bridge with bulbous nasal tip, smooth philtrum, and thin vermilion border (Fig. 4). Laboratory studies included: chromosome analysis (46,XX), FISH subtelomere analysis (normal), DNA testing for the GJB2 gene (normal); thyroid function studies (normal), and renal ultrasound (normal). Molecular microarray procedures utilizing genomic DNA extracted from peripheral blood and hybridized with normal reference DNA to Spectral Chip 2600 (1MB) was performed and detected no abnormalities in DNA from this specimen.
At 9 months of age, Patient 2 developed a pericardial effusion, which resolved by 11 months of age. Echocardiogram was negative for cardiomyopathy or structural heart defects. She had multiple episodes of otitis media and several sets of PE tubes, as well as a tonsillectomy and adenoidectomy. Bilateral cochlear implants were placed at 14 months of age. Follow-up physical examination at 17 months of age documented her height at 80.2 cm (50–75th centile), weight 9.73 kg (10th centile), and OFC 47.5 cm (75–90th centile). She had persistently open anterior fontanelle measuring 2 cm in diameter, curly blonde hair, tall forehead with bitemporal narrowing, esotropia, flat nasal bridge, low-set posteriorly rotated ears (Figs. 5A,B). At 21 months of age, a skeletal survey showed enlarged cranium with deformity of the sella, but no other defects were identified.

Patient 2 was diagnosed with seizure disorder at 4 years of age. She presented with head drop, eye deviation, and absent gaze. EEG was markedly abnormal. She has been treated with Depakote. Repeat EEG was “mildly abnormal” with sharpened slow burst activity consistent with seizure disorder, but there was marked improvement compared to the previous study. Developmentally, she has significant delays, especially in speech and communication. She uses a few signs, numbering about three to four and says four words including “mama, help, go, and eat”.

Fig. 2. Patient 1’s mother at 23 years of age. A. Frontal view. B. Lateral view.

FIG. 2. Patient 1’s mother at 23 years of age. A. Frontal view. B. Lateral view.
She is also working with a picture board. She is able to throw a ball, but she cannot count or dress herself. She does not know her colors and cannot ride a bike yet. She has not had a formal developmental assessment done, but she reportedly functions at about a 2-year level with global delays at chronological age of 4 years. She has mild behavioral problems with occasional temper tantrums, most of which are associated with her inability to communicate.

On physical examination at 4 years, her facial findings are similar to those seen in Figure 5; height 101.0 cm (20th centile), weight 15.0 kg (10–25th centile), OFC 50.0 cm (50–75th centile). Her anterior fontanelle has closed. She has a flat nasal bridge consistent with the so-called “Binder syndrome” or nasomaxillary hypoplasia. Measurements were IC 25 mm, OC 70 mm, PF bilaterally 23 mm, left esotropia. She holds objects close to her face to visualize them. The ears were low-set and had mild asymmetry in length (right 48 mm and left 52 mm). Her chest had no deformity. The right hand had normal palmar creases and the left had a bridged crease. The feet had mild 2–3 toe syndactyly. No bowing or shortening of her limbs was noted.

**DISCUSSION**

Cataracts and hearing loss can occur as major findings in multiple disorders caused by teratogenic exposures, chromosomal and metabolic abnormalities, as well as disorders with single gene inheritance [Bader et al., 1985; Begeer et al., 1991; Guala et al., 1992; Nadol and Burgess, 1982; Nucci and Mets, 1990]. These include disorders such as Stickler syndrome, rhizomelic chondrodysplasia punctata, mannosidosis (alpha B), Zellweger syndrome, and fetal rubella syndrome; however, these patients lacked other key manifestations of these disorders.

Upon review of multiple syndromes with congenital cataracts and hearing loss these two cases most closely resembled the two patients reported by Gripp et al. [1996, 1997]. Table I compares the findings of these four patients. All four patients had short stature, skeletal abnormalities (shortened arm span, bilateral radioulnar synostosis, and idiopathic chondrolysis), large, persistently open anterior fontanelle and CNS abnormalities (ventriculomegaly and Chiari I malformation), in addition to the developmental delay, congenital cataracts, and sensorineural hearing loss.

The distinctive facial appearance seen in the patients reported by Gripp et al. [1996], likened to that seen in Down syndrome, was also evident in our patients, especially in infancy. All these patients had findings similar to “Binder syndrome” with flattened facies and short nasal bridge, in addition to tented upper lip, upslanting palpebral fissures, and low set positioning of the ears with squared appearance.

Ayme and Philip [1997] later suggested that the patients described by Gripp et al. [1996] did not have a new syndrome, but resembled those patients reported by Suthers et al. [1993], Preus et al. [1984], and them [Ayme and Philip, 1996], all of whom had similar findings to the original reported case of Fine and Lubinsky [1983]. They proposed that these six patients, including those reported by Gripp et al. [1996] be described as having Fine-Lubinsky syndrome. All these patients had cataracts, hearing loss, flattened facies, prominent frontal bone, brachycephaly, and mental retardation. However, the patient described by Fine and Lubinsky [1983] had “cloverleaf” appearance to the skull without radiological evidence of craniosynostosis, severe growth
with height <5th centile (50%), and dysmorphic craniofacial features (>49%). In those patients with relatively small deletion breakpoints, the chromosomes were usually derived from the father with only one case having a deletion inherited from the mother, who also had the deletion. Information was not provided on the actual breakpoints.

All these patients seem to have larger terminal deletions of chromosome 11 than Patient 1 and his mother. Patient 1 does not have the classical findings of Jacobsen syndrome including thrombocytopenia and congenital heart defect. He does have dysmorphic craniofacial findings, but they are different from the patients reported with Jacobsen syndrome, and more like those patients described by Gripp et al. [1996, 1997]. Patient 1’s mother presented with similar craniofacial features to him, short stature and mental retardation, but lacked cataracts and hearing loss. In addition, Patient 1 has unique findings not typically reported in 11q terminal deletion syndrome, including bilateral cataracts and bilateral sensorineural hearing loss. There was only one report of a child with 11q24.2 deletion, who had hearing loss and osteopenia [Giampietro et al., 2006], and in a review of ocular manifestations of Jacobsen syndrome, there was only 1 patient with a nuclear cataract [Miller et al., 2006].

Therefore, this patient’s findings are atypical for Jacobsen syndrome and more consistent with the patients reported by Gripp et al. [1996, 1997]. The 11q25 subtelomere deletion found in Patient 1, with notable findings similar to Patient 2 and to the other two patients [Gripp et al., 1996, 1997] suggests that the etiology for this syndrome of cataracts, deafness, and Down syndrome-like facies may be caused by haploinsufficiency of a gene localized to the subtelomere region of 11q or by microdeletion of 11q in those patients not tested. The review of additional reported cases and future molecular genetic studies

<table>
<thead>
<tr>
<th>Clinical findings</th>
<th>Present Patient 1</th>
<th>Present Patient 2</th>
<th>Reported patients—Gripp et al.</th>
<th>Total number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developmental delay/mental retardation</td>
<td>+</td>
<td>+</td>
<td>2/2 (Febrile)</td>
<td>4/4 (100%)</td>
</tr>
<tr>
<td>Seizure disorder</td>
<td>—</td>
<td>—</td>
<td>1/2 (100%)</td>
<td>2/4 (50%)</td>
</tr>
<tr>
<td>Short stature</td>
<td>+ (10 Centile)</td>
<td>+ (10–20 Centile)</td>
<td>2/2 (&lt;5 Centile)</td>
<td>4/4 (100%)</td>
</tr>
<tr>
<td>Bilateral congenital cataracts</td>
<td>+</td>
<td>+</td>
<td>2/2 (Bilateral)</td>
<td>4/4 (100%)</td>
</tr>
<tr>
<td>Sensorineural hearing loss</td>
<td>+ (Bilateral)</td>
<td>+ (Bilateral)</td>
<td>2/2 (Bilateral)</td>
<td>4/4 (100%)</td>
</tr>
<tr>
<td>Short nose; flattened nasal bridge; upslanting palpebral fissures; low-set ears</td>
<td>+</td>
<td>+</td>
<td>2/2</td>
<td>4/4 (100%)</td>
</tr>
<tr>
<td>Skeletal abnormalities</td>
<td>+ (13 Ribs, large fontanelle)</td>
<td>+ (Enlarged cranium; deformity of sella)</td>
<td>2/2 (Bilateral radioulnar synostosis; late fontanelle closure; J-shaped sella (pt 1); idiopathic chondrolysis (pts 1 &amp; 2))</td>
<td>4/4 (100%)</td>
</tr>
<tr>
<td>CNS (brain imaging)</td>
<td>Prominent ventricles and cavum vergae</td>
<td>Prominence of ventricular system</td>
<td>Chiori I malformation (pt 1); mild ventricular dilatation (pt 2)</td>
<td>4/4 (100%)</td>
</tr>
<tr>
<td>Other</td>
<td>Patent ductus arteriosus</td>
<td>Pericardial effusion</td>
<td>Diaphragmatic hernia; pericardial effusion (pt 1); inguinal hernia (pt 2)</td>
<td>4/4 (100%)</td>
</tr>
</tbody>
</table>

TABLE I. Summary of Clinical Findings in Four Patients
may help clarify the clinical spectrum of this syndrome, as well as its etiology.

REFERENCES


