CASE REPORT

Lenz-Majewski Syndrome Associated with Hydrocephalus and Multiple Congenital Malformations

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ABSTRACT

Lenz-Majewski syndrome is a congenital progressive skeletal disorder hallmarked by craniotubular hyperostosis, ectodermal dysplasia (cutis laxa and enamel hypoplasia) and hand/foot osseous dysgenesis or hypoplasia (brachysyndactyly, absent metacarpals, etc). So far, only ten cases of this syndrome have been described in literature. We present the eleventh case of Lenz-Majewski syndrome with craniotubular hyperostosis cutis laxa, brachysyndactyly, hypoplastic fingers and toes and an absent metatarsal in a Hispanic boy. Notable secondary phenotypic presentations were megalocornea and glaucoma, obstructive sleep apnea, laryngotracheobronchomalacia and severe hydrocephalus with intracranial hypertension requiring shunt placement. As far as we are aware, the latter features have not been previously reported with Lenz-Majewski syndrome. The present report demonstrated the variance associated with the secondary phenotypic burden of this syndrome. Biomed. Int. 2013; 4: 45-52. ©2013 Biomedicine International, Inc.

Key words: Congenital, head, malformation, skeletal, skin

INTRODUCTION

In 1969, Braham described a pediatric patient with several congenital features similar to Camurati-Engelmann syndrome, symmetric hyperostotic disorder associated with unusual features of progeria, widened ribs, jaw affection, enamel hypoplasia, webbed hands and brachysyndactyly. This patient was revisited by Macpherson who also suggested it to be considered “a completely different” condition than Camurati-Engelmann syndrome. A strikingly similar pediatric patient characterized by growth retardation, progeria, choanal atresia, symphalangism, enamel hypoplasia and craniodiaphysial hyperostosis was later reported by Lenz and Majewski. The constellation of malformations hallmarked by craniotubular hyperostosis, ectodermal dysplasia and brachysyndactyly was then further emphasized as a distinct entity. So far, this syndrome, which should be appropriately referred to as Lenz-Majewski syndrome, has only ten reported cases in the English-language literature. The cases have been sporadically reported from North America, Europe, and Southeast and Far East Asia. Herein, the authors describe an additional patient with...
Lenz-Majewski syndrome associated with multiple unrelated congenital malformations, which may further extend the phenotypic description of this syndrome. Special emphasis is made on the course and management of communicating hydrocephalus observed in the present patient.

**CASE REPORT**

A 22-month-old Hispanic boy was brought by his mother to our center with swelling over the back of his head of one-day onset. A history of accidental head trauma due to fall 3-4 days prior to the presentation was obtained from the mother. Initial CT scan revealed a left frontal small epidural hematoma (<4 mm in width), bilateral posterior subgaleal accumulation, cortical atrophy and ventriculomegaly (**Figure 1**). On examination, the patient was alert and reactive with developmental delay. Multiple facial and limb abnormalities were noted (**Figures 2 and 3**). The head was large with notable frontal bossing and an open, full anterior fontanelle. The skin was lax and wrinkled with excessive subcutaneous fat. Subcutaneous veins were readily visible, especially over the forehead and scalp. Large palpebral fissures and slightly bulged eyes were also noted.

![Figure 1: Non-contrast head CT scan. Although left frontal epidural hematoma and bilateral posterior subgaleal accumulations are acute in appearance, frontotemporal gyral atrophy, widened subarachnoid space and sulci, and enlargement of lateral ventricles represent a chronic condition.](image)

The past medical history revealed an otherwise uncomplicated vaginal delivery. Mother had routine prenatal care and uncertainly stated that the age of biological father was approximately 25 years at the time of conception. Bilateral cryptorchidism, skeletal abnormalities, progeria-like appearance and redundant skin had been noted in early infancy. The early-infancy skeletal X-ray survey had shown generalized osteopenia, diffuse diaphyseal sclerosis, metaphyseal lucency, frontal bone sclerosis, widened clavicles, ribs and ischia, hypoplastic metatarsals and metacarpals and bilateral absence of one metatarsal, consistent with the clinicoradiological diagnosis of Lenz-Majewski syndrome. Head CT scans had demonstrated slight prominence of extra-axial spaces and enlarged basilar cisterns at 2-months of age, and mildly dilated lateral and third ventricles and prominent sulci and cisterns at 4-months of age. A small patent ductus arteriosus, patent foramen ovale, mildly dilated right atrium and ventricle were noted on initial echocardiography but later re-
The patient underwent surgery for choanal atresia and nasolacrimal duct obstruction as well as small bowel resection and ileostomy creation due to necrotizing enterocolitis-related bowel adhesions and stricture formation in early infancy. This was followed by closure of ileostomy and laparotomy with Roux-en-Y feeding jejunostomy for gastric inertia and feeding intolerance at 6 and 11 months of age, respectively. At 7-months of age, an ocular examination under anesthesia revealed bilateral congenital glaucoma and megalocornea. A skeletal X-ray survey at 14-months of age had revealed diffuse skeletal dysplasia, osteosclerosis and osteopenic appearance; the characteristic findings were craniofacial disproportion with bulbous calvarial contour, frontal prominence and midface dysplasia, widened ribs and clavicles, osteosclerosis and undertubulation of the long bones in the upper and lower extremities and hypoplasia of metacarpals, hand and foot phalanges and bilateral absence of one metatarsal. A repeat head CT scan at 14-months also had demonstrated increased dilation of the lateral and third ventricles compared to a scan performed at 4 months. At 17-months, the patient underwent bilateral myringotomy tube placement for chronic otitis media and mucoid effusions, which was complicated by postoperative pneumonia, respiratory failure and obstructive sleep apnea. A bronchoscopy at that time revealed pharyngeal hypotonia (perhaps due to decreased muscular tone and/or connective tissue disorder), laryngomalacia and tracheobronchomalacia. He underwent a nasal septoplasty for a deviated septum and severe nasal obstruction at 19 months, and continued to receive nighttime bilevel positive airway pressure (BiPAP) for obstructive sleep apnea.

Figure 2: Patient’s facial features upon presentation with hydrocephalus (2a) and at 50 months of age (2b). 2a, Progeroid appearance, frontal bossing with visible subcutaneous veins, hypertelorism, depressed nasal bridge and broad nasal tip, flared nares, malformed ears, and thickened upper lip are remarkable. 2b, Note the box-shaped head.

With a diagnosis of hypertensive hydrocephalus, the patient then underwent a right ventriculoperitoneal shunt insertion at 22 month of age. Notable during subcutaneous tunneling for shunt placement was significant venous engorgement and abnormally dense connective tissues. Significant collapse of his ventricles was noted on the repeat head CT scan 9 days later. Repeat CT scans also revealed narrowing of the foramen magnum, which could potentially explain the occurrence of hydrocephalus in this patient. Unfortunately, 8 months later, the patient presented with a wound dehiscence, shunt infection and subse-
quent formation of subdural empyema. The shunt was removed; an external ventricular drain was placed. The postoperative course was complicated by formation of a subdural empyema, which was managed by left frontal small craniotomy and irrigation. Eventually, an occipital ventriculoperitoneal shunt was inserted. A follow-up CT scan three months later showed interval decompression of the lateral ventricles. Five months later the patient was readmitted for symptoms of shunt failure consisting of bradycardia and apneic spells and underwent emergent external ventricular drain placement. The hospital course was complicated by intraparenchymal and intraventricular hemorrhages associated with catheter placement, failure after shunt re-insertion and development of ventriculitis requiring prolonged external ventricular drainage and antibiotic therapy. Technical challenges related to the underlying syndromic features such as thin skin and dense soft tissue were encountered with these surgeries. Eventually, a shunt was replaced and the patient was discharged home. Within a few days, he had to be readmitted for recurrent shunt failure and respiratory failure requiring ventilator support and tracheostomy placement. At this point the patient had a shunt reinserted but was not discharged from the hospital due to persistent respiratory issues and sepsis. A repeat hand and foot X-ray was performed at 48 months of age, which in comparison to an earlier X-rays (Figure 4) showed the severely progressive nature of osteosclerosis (Figure 5).

Figure 3: Photographs of right (3a) and left hands (3b) and right (3c) and left feet (3d) at 50-51 months of age (note that earlier images were of low-quality and are not shown here). Wrinkled skin, brachydactyly, cutaneous syndactyly, hyperconvex nails, and short foot with dorsiflexed toes are remarkable.
Figure 4: Skeletal X-rays (at 22 months of age) showing osteosclerosis of skull base and orbital rim and midface hypoplasia (a), osteosclerosis of long bones, metaphyseal lucency and bilateral agenesis of a metatarsal and undermodeling/hypoplasia of metatarsals and toe phalanges (b, c and d), and widened ribs (e).

Figure 5: Hand and foot X-ray at 48 months of age. Severely progressive osteosclerosis is evident in comparison to Figure 4. Brachydactyly, symphalangism, phalangeal hypoplasia, underdeveloped carpal bones (A), epiphyseal/metaphyseal lucency, sclerotic and thickened cortical bone (B), and absent metatarsal and underdevelopment of tarsal bones (C) are remarkable.
DISCUSSION

Lenz-Majewski syndrome is a distinct form of craniotubular bone dysplasia characterized by progressive craniotubular hyperostosis and osteosclerosis (thickened calvaria, ribs, and diaphyseal bones), ectodermal dysplasia (e.g., enamel hypoplasia, cutis laxa), proximal symphalangism/syndactyly and disproportionate brachydactyly. Proximal symphalangism is often associated with interdigital webbing or cutaneous syndactyly. Characteristic skeletal finding of Lenz-Majewski syndrome were present in our patient, although abnormalities of foot (e.g., absent metatarsal) were more dominant than hands (Figures 4 and 5). A Lenz-Majewski syndrome-like syndrome has also been reported in a Japanese boy with limited tubular osteosclerosis, and rather-proportionate shortening of the digits without symphalangism. The 2006 revised edition of Nosology and Classification of Genetic Skeletal Disorders included this syndrome (together with such syndromes as Camurati-Engelmann, Tricho-dento-osseous dysplasia, Pachydermoperiostosis, etc.) under the category of increased bone density with metaphyseal and/or diaphyseal involvement. The genetic basis of Lenz-Majewski syndrome is still unknown and chromosomal studies have failed to show a gross abnormality; however, several patients reported previously had been associated with older paternal age. Although such an association cannot be fully justified based on the limited reports, one may refer to other congenital skeletal malformations associated with advanced paternal age such as achondroplasia and acrocephalosyndactyly, potentially linked to increased likelihood of mutation in the aged spermatozoon. Notably, the family history was positive for a sibling with Down syndrome in the patient described by Braham and Macpherson. The prognosis of Lenz-Majewski syndrome is often poor due to multiple and progressive congenital deformations, failure to thrive and developmental delay. The patients may die early in the neonatal period, or as Majewski noted, may survive until adulthood with no serious illness. Heterogeneous presentations and non-classic findings in Lenz-Majewski syndrome have been reported by previous authors. Cerebral agenesis and micrognathia, cryptorchidism, lumbar spina bifida occulta and hemivertebrae, ambiguous genitalia, hypoplasia, Chordee, exophthalmia, communicating hydrocephalus, cleft palate, persistent peripheral facial palsy, choanal stenosis, hip dysplasia and strabismus, humero-radial synostosis, nasolacrimal duct obstruction, dysgenesis of corpus callosum and mild white matter atrophy, prognathism, and conductive hearing loss have also been reported. In a postmortem examination by Kaye and colleagues no gross abnormality was noted in the internal organs including brain. Lenz-Majewski syndrome is in differential diagnosis of a group of genetic skeletal disorders which are associated with hyperostosis and diaphyseal dysplasia. A classic example is Camurati-Engelmann’s syndrome, a progressive tubular bone dysplasia. In a previous report, enamel hypoplasia, abnormal modeling of long bones and cutaneous abnormalities such as cutis laxa have been described as parts of the so-called SCARF syndrome. However, involvement of hands and feet (e.g., symphalangism, brachysyndactyly and absence or hypoplasia of the small bones) in association with craniodiaphyseal hyperostosis (dysplasia) is characteristic for Lenz-Majewski syndrome.

Table 1 compares the clinical feature of the present patient and the one originally described by Lenz and Majewski. The present patient had characteristic clinicoradiological features of Lenz-Majewski syndrome including cutis laxa, craniotubular hyperostosis and brachydactyly. He additionally had an absent metatarsal. Other notable malformations
were communicating hydrocephalus (secondary to skull base hyperostosis and narrowing of the foramen magnum, impairment of cerebral venous outflow or decreased cerebrospinal fluid absorption), glaucoma and megalocornea (perhaps due to excess laxity of corneal stroma), cryptorchidism (due to gubernacular connective tissue changes) and laryngotracheobronchomalacia. A mild dilatation of lateral ventricles was also reported by Gorlin and Whitley in a patient with no evidence of intracranial hypertension and no need for intervention. Macrocephaly and mild dilatation of lateral ventricles were described in a Japanese boy with atypical Lenz-Majewski syndrome characterized by mild undertubulation of metacarpals and proximal phalanges and dominantly metaphyseal involvement of tubular bones; no intervention was reported for mild hydrocephalus. In a patient with communicating hydrocephalus, Wattanasirichaigoon and colleagues reported a good response to carbonic anhydrase inhibitor, and attributed the cause of hydrocephalus to an impaired intracranial venous drainage and cerebrospinal fluid absorption.

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<th>Table 1: Comparison of clinical features of the present patient with the original report of Lenz and Majewski (1974)</th>
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<td>Obstructive sleep apnea</td>
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Ultimately, the present report added a new case of Lenz-Majewski syndrome to the extant literature. Aside from typical features of the syndrome, novel associations with this rare syndrome included hydrocephalus with intracranial hypertension requiring shunt placement, glaucoma/megalocornea as well as laryngotracheobronchomalacia leading to obstructive sleep apnea. As far as we are aware, the latter features have not been previously reported with Lenz-Majewski syndrome. In agreement with previous reports, our report demonstrated the variance associated with the secondary phenotypic burden of this syndrome.

REFERENCES