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Open and Closed Lip Schizencephaly in Seckel Syndrome: A Case Report

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Abstract

Seckel syndrome (Online Mendelian Inheritance in Man database Number 210600) is the classic prototype of primordial bird-headed dwarfism. In addition to the characteristic craniofacial dysmorphism and skeletal defects, abnormalities of the cardiovascular, hematopoietic, endocrine, and central nervous systems are described. The full phenotypic spectrum of this clinically and genetically heterogeneous syndrome is yet to be delineated. Presented herein is a boy 2 years and 5 months old, with Seckel syndrome, born to second-degree consanguineous Muslim parents. In addition to the classic phenotype of the disorder, this patient had both, an open and a closed lip schizencephaly detected on cranial computed tomography (CT) scan. To our knowledge, the association of schizencephaly and Seckel syndrome is not described previously in the English language literature. In addition, presented briefly is a review of the anatomical cerebral cortical malformations associated with this syndrome.

Keywords

Septum pellucidum, seckel syndrome, schizencephaly, consanguinity

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Seckel syndrome (Online Mendelian Inheritance in Man database Number 210600) is a rare form of primordial dwarfism, which was initially described in 1960.[1] Since the initial description, more than 60 cases are reported; however, less than one third appear to fulfill the criteria originally set forth by Seckel.[2] Among the generally accepted minimal criteria are severe intrauterine and postnatal dwarfism; severe microcephaly with mental retardation; and facial anomalies, including a receding forehead and chin, large beaked nose, and large or bulging eyes.[1] Presented herein is a child with classic Seckel phenotype, who had both an open and a closed lip schizencephaly, resulting in global developmental delay and bilateral sensorineural deafness.

Case Report

A 2-year 5-month-old boy, born to a 28-year-old second-degree consanguineous Muslim mother, was initially seen for his unusual "facial appearance," small body stature, and for possible evaluation of developmental delay. He was born by spontaneous vaginal delivery at term and had an uneventful immediate postnatal period. The mother had 2 episodes of spontaneous miscarriage at 12th and 16th weeks of gestation in the past. She had an uneventful present pregnancy, without exposure to unusual medications, radiation, or trauma. A single antenatal ultrasound performed at 16 weeks of gestation was reportedly normal. The birth weight, length, and the head circumference of the baby were 1800 g, 37 cm, and 28 cm, respectively (all much below the third percentile). At presentation, he weighed 4250 g and stood 53 cm tall (both being significantly below the third percentile). The anthropometry revealed the following values: upper body segment to lower body segment ratio: 1.1; head circumference: 31 cm; arm span: 51 cm; upper limb length: 18 cm bilaterally with upper segment to lower segment ratio of 0.85; midarm circumference taken midway between the tip of acromian and the olecranon process: 7.5 cm bilaterally. The ratio of upper leg segment to the lower leg segment was 1.15. The chest and the abdominal circumference were 30.5 and 31 cm, respectively. The phenotype revealed a small head with sloping forehead, completely fused anterior and posterior skull fontanel with sutural ridges, relative micrognathia, bilaterally low-set ears, high-arched palate, prominent aquiline nose (Figure 1), bilateral fifth finger clinodactyly, partial cutaneous syndactyly of the left second and third toes, and cryptorchidism. Systemic examination did not

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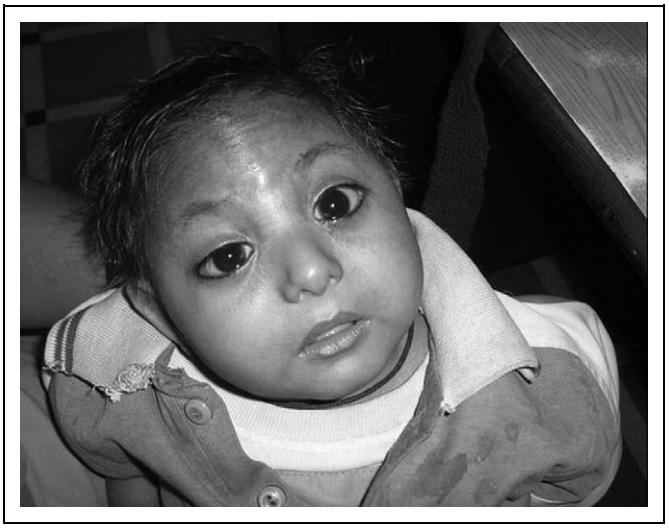

Figure 1. Severe microcephaly, receding forehead, prominent aquiline nose and micrognathia, giving rise to the typical "bird-head" appearance, characteristic of Seckel syndrome.

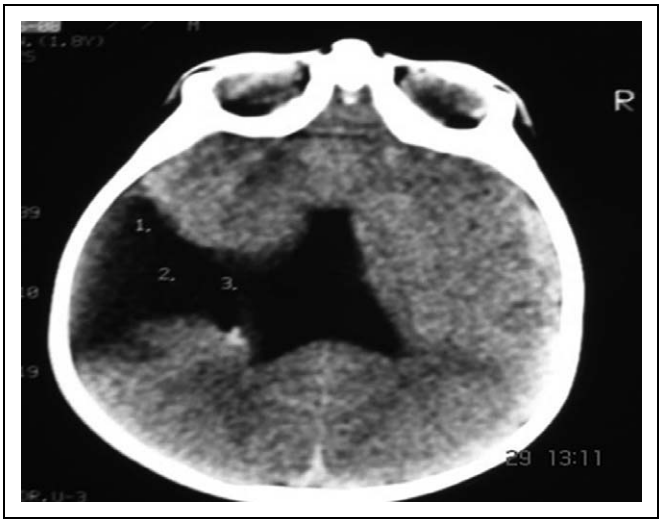

Figure 2. Cranial computerized tomography (CT) scan showing absent septum pellucidum and open-lip schizencephaly in the left temporo-frontoparietal cerebral convexity, communicating with the ipsilateral lateral ventricle.

reveal any abnormality. The assessment of the individual domains of developmental milestones revealed the following: gross motor, 7 months; fine motor, 10 months; cognition, 9 months; language, 8 months; social/emotional, 9 months; and feeding, 10 months. The relevant hematological investigations, chest radiograph, and abdominal ultrasound were normal. The bone age was calculated to be 12 months. No skeletal anomalies were identified on skeletal survey. The Brainstem Evoked Response Audiometry revealed mild sensorineural deafness in both ears and the formal ophthalmological screen was noncontributory. The karyotype was consistent with a normal male phenotype. Cranial computed tomography (CT) scan showed absent septum pellucidum and open-lip schizencephaly in the left temporo-frontoparietal

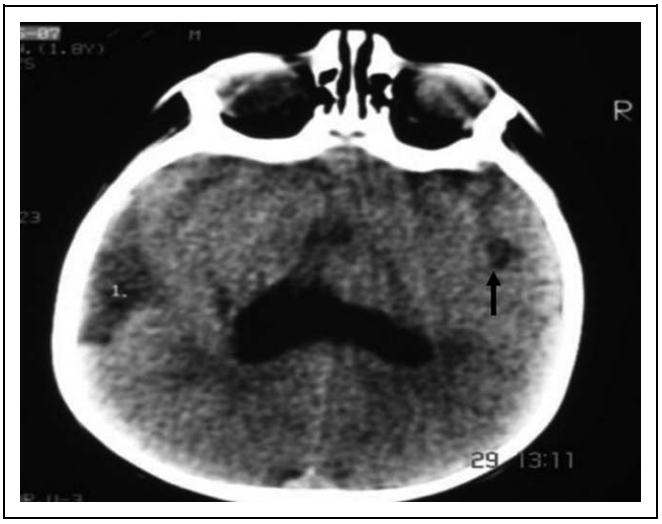

Figure 3. Cranial computerized tomography (CT) scan showing small closed-lip schizencephaly in the right frontoparietal area (arrow).

cerebral convexity, communicating with the ipsilateral lateral ventricle (Figure 2). A small closed-lip schizencephaly in the right frontoparietal area was also noted (Figure 3).

Discussion

Cerebral cortical malformations are increasingly recognized and reported in Seckel syndrome. In the last several years, various descriptions of cerebral cortical malformation have been reported. These malformations possibly explain both mental retardation and neurologic signs that are almost always present in this syndrome. It has been observed that the differences in clinical expression in Seckel syndrome can be explained by different types of cortical dysplasia noted in such patients.

The first report of central nervous system anomalies in this syndrome was provided in 1967 by McKusick et al,[3] when they described 3 affected siblings, 2 of which had neuropathologic evidence of cerebral dysgenesis at autopsy. Hori et al[4] described in a preterm Seckel neonate, a near-complete agyria with sparing of the parieto-occipital sulcus. The neonate had markedly reduced brain weight. Additional observations were the presence of multiple arachnoid cysts and corpus callosal agenesis. Histopathological examination of the cortical cell layers revealed irregularly distributed neuroblasts with heterotopic collections of neurons in the white matter. In the periventricular region, subependymal matrix cells were decreased and seen only in the stria terminalis. Recently, we cared for an 8-year-old boy with Seckel syndrome, who had agenesis of the corpus callosum with cerebellar tonsillar herniation, which resulted in mirror movements of his arms.[5] A small cerebrum with poor convolutional markings, comparatively large cerebellum, and a possible congenital, midline arachnoid cyst was reported by Krishna et al[6] in a 28-year-old Yemeni woman with Seckel syndrome born to second-degree consanguineous parents. Polymicrogyria in such

children has also been described.[7] A 2-month-old affected infant[8] demonstrated hypoplastic cerebrum and cerebellum, which resulted in a largely empty intracranial space. A review[9] found a family with the disorder and corpus callosal agenesis along with cerebral dysgenesis, in addition to cerebellar vermal hypoplasia, pachygyria, and a medially located dorsal cyst. Severe hydrocephalus in 3 siblings, with 2 having congenital arachnoid cysts is also reported.[10] Another 9-year-old child with Seckel syndrome and enlarged cerebral ventricles was reported by Howanietz et al.[11] Recently, a report[12] described 3 new cases of different malformations of cortical development (one with gyral hypoplasia, another with macrogyria and partial corpus callosum agenesis, and yet another with bilateral opercular macrogyria). The first report of semilobar holoprosencephaly in Seckel syndrome was provided by Kumar et al[13] in a 24-day-old male neonate, who presented with seizures since birth. The baby also had an extra-axial cyst that communicated with the body of right lateral ventricle in the temporoparietal region.

At the fundamental level, Seckel syndrome remains a disorder of cellular proliferation. It is known that most instances of Seckel syndrome are caused due to mutations in the ataxia telangiectasia and Rad3-related protein.[14] This protein has been shown to play a pivotal role in embryonic development and somatic cell proliferation.[15] Such mutations have been directly attributed to be responsible for the clinical manifestations such as microcephaly, severe pre- and postnatal growth retardation and short stature.

To our knowledge, association of schizencephaly, either "isolated" or co-occurring with other cerebral cortical malformations in Seckel syndrome, has not been reported till date. This report reiterates the extreme clinical heterogeneity observed in this syndrome and supports the fact that cerebral cortical malformations constitute important integral findings.

Declaration of Conflicting Interests

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