Seckel-like syndrome or Seckel variants?

Mathew Punnachalil Cherian MD, DCH, FRCPI

From the Ras Tanura Health Center, Saudi Aramco Medical Services Organization, Ras Tanura, Saudi Arabia.

Correspondence to:
Dr. Mathew P. Cherian
Saudi Aramco
P.O. Box 1356
Ras Tanura 31311
Saudi Arabia
E-mail: mathew.cherian@aramco.com

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Seckel syndrome, first defined by Seckel in 1960,[1] is characterized by microcephaly, proportionate dwarfism of prenatal onset, and a typical "bird-headed" profile (beaked nose, receding forehead, prominent eyes and micrognathia). Various other facial and skeletal abnormalities have been documented by subsequent authors, including low-set ears with hypoplastic lobules, premature closure of cranial sutures, fifth finger clinodactyly, dislocation of radial heads and, eleven pairs of ribs.[2-5] The clinical delineation of this syndrome has been inconsistent even using Seckel's original criteria. Majewski reviewed the literature and found that two-thirds of the reported cases did not meet all the diagnostic criteria proposed by Seckel.[2] In addition to the bird-headed profile and skeletal anomalies, abnormalities have been found in cardiovascular, hematopoietic, and endocrine as well as nervous systems. Mental retardation is not as marked as might be expected in view of the very small brain. Recently, cases are being reported as Seckel-like syndrome: the first report, a child with unusual appearance of hands and feet;[4] and a second report of three siblings with severe hydrocephalus.[5]

The mode of inheritance in Seckel syndrome is thought to be autosomal recessive. Advances in molecular genetics in recent years have shown some aberration in a few chromosomes; however, a definite diagnostic genetic defect has not been found so far. The rarity of the syndrome, lack of a definite diagnostic test, frequent phenotypic variability as well as the recent finding of involvement of different chromosomes have resulted in confusion and debate over exact definition of this condition.

Three girls of a Saudi Arabian family with pre-natal and post-natal growth retardation, characteristic cranio-facial dysmorphism, proportionate short stature and some of the skeletal anomalies of Seckel syndrome are presented in this report. Their parents are first cousins, supporting an autosomal recessive mode of inheritance. There is no history of a similar condition in other family members.

Case 1

A 17-year old girl (Figure 1), the oldest of three sisters, a product of an uneventful pregnancy, was born full-term to consanguineous Saudi parents with a birth weight of 2000 grams, a length of 46 centimeters and a head circumference of 31 centimeters. At birth, she was found to have a beaked nose and retrognathia. Her developmental milestones were significantly delayed. She sat at 9 months, stood with support at 17 months and started walking at 21 months. She attended a special school until 15 years of age, but school was terminated because of academic failure. Her speech and language were significantly delayed. On her clinic visits, she exhibited significant growth retardation with weight and height remaining far below the third percentile, microcephaly, and characteristic cranio-facial dysmorphism, including receding forehead, hypotelorism, beaked nose, crowded teeth and micrognathia. The ears were low-set and lobes underdeveloped. She had clinodactyly of the fifth fingers as well as medial deviation of the left second and third toes. She showed evidence of moderate to severe mental retardation. She could comprehend simple commands and communicate with some basic words, but speech was unintelligible. She was generally shy though there were occasional temper tantrums. Results of routine hematological and biochemical tests were normal. Her karyotype was 46, XX. Detailed chromosomal analysis was performed and thirty metaphases were studied. The proportion of cells with chromosome breakage was comparable to a parallel control. Results of the mitomycin C stress test (50 ng/mL of MMC for 48 hours) with particular attention to radial formations were within normal limits. A skeletal survey showed incomplete segmentation of the mid-thoracic spine associated with minimal scoliosis. The bone age was retarded. CT scan of brain showed no intracranial abnormality.

Case 2

A 14-year old girl (Figure 2), a product of a full-term pregnancy, was born in an ambulance as an undiagnosed first twin with a birth-weight of 2460 grams, a length of 43 centimeters and a head circumference of 32 centimeters (the second twin, delivered along with the placenta, was dead, shrunk and mummified, weighing only 160 grams). At birth, she had scaly parchment-like skin as well

as a prominent beaked nose. Subsequently, she showed significant delay in neurodevelopment and more cranio-facial dysmorphism. She had microcephaly, a receding forehead, a beaked nose, micrognathia, malformed large ears with absent ear lobules, hypotelorism, high-arched palate, bifid uvula, mild clinodactyly of the fifth fingers and enamel hypoplasia. The thorax was of narrow frame associated with pectus excavatum. Examination of the skeletal system showed three small-sized toes on both feet as well as varus flexion-deformity of the middle and distal phalanges of the third toe of the right foot. At 8 years, she was referred to the pediatric psychiatrist because of extreme shyness, inadequate social behavior, poor communication skills and school failures. Her IQ was around 45. She played mostly alone, but exhibited frequent temper tantrums and occasional aggressive behavior. Routine laboratory work up was normal. Chromosome karyotype was 46, XX. There was no chromosomal breakage; the mitomycin C stress test was unremarkable. Her skeletal survey was normal except for varus flexion deformity of the middle and distal phalanges of the third toe of the right foot. A CT of the brain showed significant dilatation of the right lateral ventricle, with mild shift of midline structures to the left side, which could indicate a partial obstructive process in the Foramen of Monroe. Prominent digital markings on the scout view seen on the inner table of the skull could be due to craniosynostosis changes.

Case 3

The youngest of the three sisters, aged 11 years (Figure 3), was born full-term following an uneventful pregnancy. Birth weight was 2500 grams, length was 46 centimeters, and the head circumference 32 centimeters. She had a characteristic bird-headed profile with a beaked nose, hypotelorism, a receding forehead, and micrognathia. The ears were large with small lobules. There was bilateral clinodactyly of the fifth fingers. The third toes of both feet were angulated showing fixed flexion of the distal phalanges. The patient's development was significantly delayed. Her speech was unintelligible and comprehension poor. She had moderate to severe mental retardation and attended a special school for the mentally retarded. Laboratory work up was unremarkable except for elevated IgE levels. Chromosome analysis showed normal karyotype. There was no chromosome breakage and mitomycin C stress tests were normal. A skeletal survey revealed mild thoracic scoliosis, bilateral symmetrical varus deformities of the third toes, and pseudo-epiphyses at proximal ends of the second metacarpal bones. Bone age was retarded. A CT scan of brain was normal.

DISCUSSION

Seckel syndrome was suspected in these three siblings of a Saudi Arabian family by the findings of intrauterine and

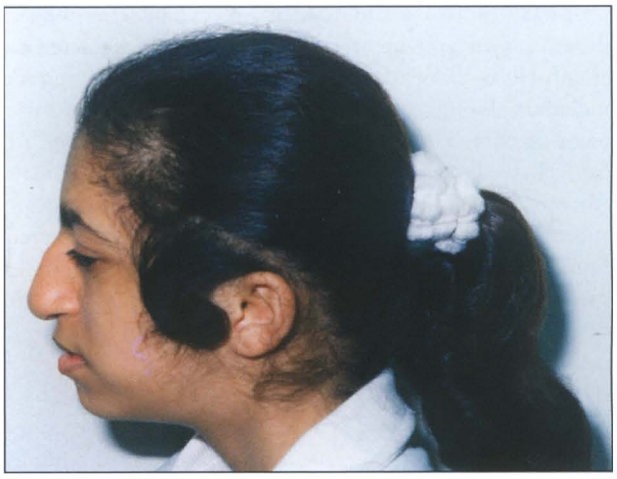

Figure 1. Case 1 showing 'bird-headed' profile.

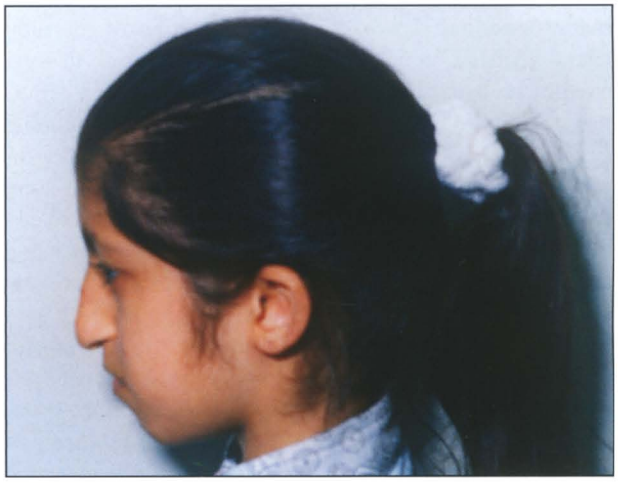

Figure 2. Case 2 showing the typical profile and absent ear lobules.

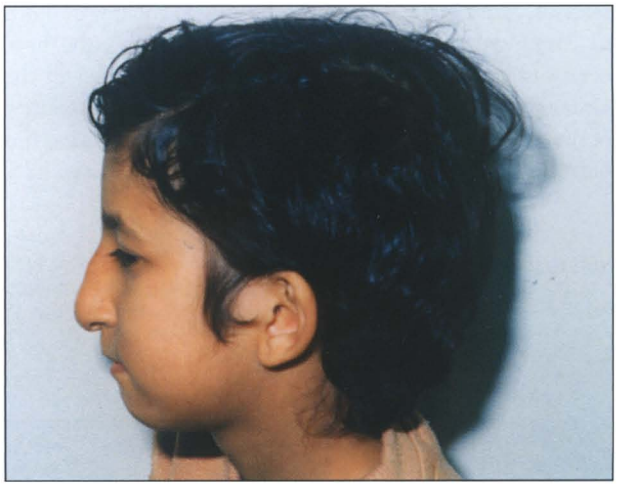

Figure 3. Case 3.

post-natal growth retardation, microcephaly, cranio-facial dysmorphism and mental retardation. The characteristic cranio-facial abnormalities, giving a "bird-headed" profile include a sloping forehead, prominent beaked nose and a receding chin. The ears were low-set, large and lobeless. All cases showed protruded eyes associated with hypotelorism. All were mentally retarded with associated significant speech and communication problems. The skeletal defects found in these children were premature closure of cranial sutures, clinodactyly of the fifth fingers, thoracic scoliosis, deformity of bones as well as pseudo-epiphysis of metacarpal bones.

Several abnormalities of the central nervous system have been described in Seckel syndrome. Arnold et al described three siblings from a Caucasian non-consanguineous family with Seckel syndrome associated with severe hydrocephalus.[5] Enlarged cerebral ventricles were found in a 9-year old child reported by Howanitz et al.[6] The second patient in my series has shown significant dilatation of the right lateral ventricle, which could be due to a partial obstructive process in the Foramen of Monroe. Other CNS defects described in Seckel syndrome include agyria and arachnoid cysts,[3,5] agenesis of the corpus callosum,[5,7] cerebral dysgenesis, and evidence of abnormal neuronal migration[3,7] and multiple intracranial aneurysms.[8] All three girls showed evidence of significant mental retardation as well as speech and language impairment. A subgroup of patients with Seckel syndrome have been described who show significant hematopoietic abnormalities, especially hypoplastic anemia and pancytopenia.[5,9] Some authors have speculated that these abnormalities could be due to increased chromosome instability or chromosome breakage similar to the DNA repair syndromes.[9] However, there was no evidence of increased chromosomal breakage in my patients and the mitomycin C stress test was negative.

The mode of inheritance is thought to be autosomal recessive. The three girls reported in this article were born to consanguineous parents. Though several reports have been published with more than one child affected in the same family, consanguinity is being reported in only a few of them.[3,7,10] The exact etiology of Seckel syndrome has not been elucidated so far. Advances in molecular genetics have been helpful to detect aberrations in a few different chromosomes, but a breakthrough finding of a definite genetic defect has not been achieved so far. Interstitial deletion of chromosome 2 has been found in at least two patients with phenotypic features of Seckel syndrome.[11] Courtens et al concluded that deletion of one or more genes in the 2 q 33.3-34 region would result in a Seckel-like syndrome.[12] MacDonald et al described a patient meeting the diagnostic criteria of Seckel syndrome, who showed interstitial deletion of chromosome 1q 22-1q 24.3.[13] Autozygosity mapping by Goodship et al in two consanguineous families of Pakistani origin with Seckel syndrome found markers, which mapped to chromosome 3 q22.1-q24.[10] O' Driscoll et al very recently showed that the individuals with Seckel syndrome in the report of Goodship et al showed a mutation in the gene encoding ataxia-telangiectasia and Rad3-related protein (ATR).[14] Borglum et al studied a consanguineous family of Iraqi descent with four affected children fulfilling the criteria of Seckel syndrome and mapped the locus to chromosome 18p11.31-q11.2, and noted a number of distinct differences between this family and individuals in the chromosome 3-linked families with Seckel syndrome.[15] In a chromosome 18-linked family, mental and motor retardation was milder and the skin showed one or more café-au-lait spots. Faivre et al confirmed the heterogeneity of Seckel syndrome by excluding the previously mapped loci on chromosome 3 and 18 in five consanguineous and one multiplex non-consanguineous Seckel syndrome families.[16]

Thus there is marked phenotypic variability in this syndrome and it appears to have several subsets, such as those with severe hydrocephalus, abnormalities of hands and feet and presence of hemopoietic abnormalities. This variability explains the controversy in the application of this diagnosis. A significant proportion of patients reported so far in the medical literature, including these three girls, may fit into "Seckel variants" or "Seckel-like syndrome".

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