

SECKEL SYNDROME IN A - 2 YEAR OLD GIRL

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ABSTRACT

Seckel syndrome is a frequent autosomal recessive that cause microcephalic osteodysplastic dwarfisms. It characterized with proportionate dwarfism of prenatal onset, dysmorphic features including severe microcephaly and "bird-headed" like appearance, mental retardation and autosomal recessive inheritance, because defect on chromosome 3q22.1-q24 (SCKL1), chromosome 18p11.31-q11.2 (SCKL2) and chromosome 14q23 (SCKL3). We reported, 2 years, 8 months female with intrauterine growth restriction, severe proportionately short stature, a "bird-headed" profile with receding forehead, large eyes, breaks like protrusion of the nose, narrow face, receding lower jaw and micrognathia and from bone survey we found a retarded bone age on which was appropriate for 6 months of age. There was no other systems disorder have been found and no specific medication has been given. Patient was hospitalized to establish diagnosis and was discharged after ten days of hospitalization. [MEDICINA 2013;44:62-68]

Keywords: Seckel syndrome, SCKL 1, SCKL 2, SCKL 3, "bird-headed" profile

SYNDROM SECKEL PADA PEREMPUAN DUA TAHUN

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ABSTRAK

Sindrom Seckel adalah sindrom autosomal resesif yang sering menyebabkan gambaran dwarfisme *microcephalic osteodysplastic*. Sindrom Seckel merupakan suatu dwarfisme proporsional dengan onset prenatal. Karakteristik sindrom Seckel adalah gambaran dismorfik antara lain: mikrosefali, wajah menyerupai kepala burung, retardasi mental, yang diturunkan secara autosomal resesif, akibat defek pada kromosom 3q22.1-q24 (SCKL1), 18p11.31-q11.2 (SCKL2), dan 14q23 (SCKL3). Kami melaporkan perempuan, 2 tahun 8 bulan dengan riwayat restriksi pertumbuhan intrauterin (berat lahir 1100 gram dan panjang lahir 25 cm), dari pemeriksaan fisik ditemukan perawakan pendek proporsional, gambaran kepala burung dengan dahi menonjol, mata besar, hidung menyerupai paruh burung, wajah yang lebar, dan mikrognatia, serta pada pencitraan ditemukan umur tulang yang sesuai untuk bayi usia enam bulan. Gangguan sistem organ lain yang menyertai sindrom Seckel tidak ditemukan. Penderita tidak mendapat terapi spesifik selama di rumah sakit. Penderita masuk rumah sakit untuk penegakan diagnosis dan dipulangkan setelah sepuluh hari perawatan. [MEDICINA 2013;44:62-68]

Kata kunci: Seckel syndrome, SCKL 1, SCKL 2, SCKL 3, "bird-headed" profile

INTRODUCTION

Seckel syndrome is a frequent autosomal recessive that cause microcephalic osteodysplastic dwarfisms. First observed on 1960 by Rudolf Ludwig Karl Virchow but first published by German Pediatrician, Helmut Paul George Seckel, at the same year. Prevalence still unknown but more than 100 cases have been reported to date.¹

Seckel syndrome is a proportionate dwarfism of prenatal onset with characteristics dysmorphic features including severe microcephaly and a bird-headed like appearance, mental retardation and autosomal recessive inheritance. Seckel syndrome is characterized by intrauterine growth restriction,² severe proportionately short stature with severe microcephaly, a "bird-headed" profile with receding forehead, large eyes, break like protrusion of the nose, narrow face, receding lower jaw, micrognathia, mental retardation; and other occasional features.³

In most cases, diagnosis depends upon recognition of clinical findings. In some cases, increased chromosomal breakage has been reported, but it was not confirmed in all cases of Seckel Syndrome and cannot be used as a tool for the diagnosis. X-ray features include retarded bone age, frequent hip dysplasia and dislocation of the head of the radius. Definitive diagnosis acquires gen analyses to find SCKL 1, SCKL 2 and SCKL 3.⁴

There is no specific treatment for Seckel syndrome. Medical treatment is depending on the symptoms.⁴ Educations for the family and patient itself have a great role for them to understand this syndrome.⁵ We reported a case of seckel syndrome.

THE CASE

DA, female, 2 years, 8 month, from Pengandang village, Praya, Central Lombok, NTB, with chief complain failed to gain weight. Patient was referred from Mataram-NTB Hospital with short stature and dwarfism. Since birth until 2.5

years of age, her height wasn't at the same majority of her mate at the same age (**Figure 1**).

Patient also can't speak fluently. She just able to say couple words like "ina", "mamak", "pak" and not yet able to speak a sentence. Most the way of communication was doing with sign language. Activities were just like other children at the same age. She responded to eye contact, shake hand, sound and situation around. She had 3-4 times/day 3-4 spoons to have. Patients have 1 glass (200 cc) of milk daily. There were no other complains i.e.: cough, common cold, nausea, vomit, diarrhea, or fever. Passing stool and urinating was normal.

On past illness history, patients had 3 episodes of simple febrile seizure, at age 13 months, 18 months and 23 months. Febrile seizures was less than 5 minutes and resolve well.

During the pregnancy her mother regularly went to public health midwife. This pregnancy was her 3rd, with history of abortion on 2nd at 6 months of pregnancy. The first one was a



Figure 1. Clockwise. 1) Picture at 11 months of age, 2) picture at 16 months of age, 3 & 4) picture at 2 years 8 months of age. A "bird-headed" profile with receding forehead, large eyes, breaks like protrusion of the nose, narrow face, receding lower jaw and micrognathia.

healthy son 13 years old. Normal delivery assisted by midwife, full term, vigorous, with birth weight and height was 1100 grams and 25 cm respectively. Midwife had referred her to hospital because her baby not normal but she refused. Her body weight was increased just 1 kg during pregnancy (43 to 44 kg). Mother's didn't suffer from any serious disease, she was not smoking, drinking alcohol, taking drugs or other medicines that received from public health midwife suggested. There was no exposure to chemical substance or high voltage electricity. There were no same complain in family, no short stature in family. Mother's height 149 cm and father's height 155 cm. potential height was 145.5 ± 8.5 (137-154 cm).

On physical examination, general appearance good, compos mentis, 3,3 kg of weight, 55 cm of height, 31 cm height in sitting position, which proportional according to age and sex for 2 years 8 months girl (U/L ratio $31/24 = 1.3$) (Figure 2), ideal body weight 4,2 kg, nutritional status 78% (moderate malnutrition with Waterlow criteria), weight for age <P-3 (P -8.23), height for age <P-3 (P -10.47), height for weight <P-3 according to WHO 2005, arm span 53 cm, left and right arm length 19 cm/19 cm respectively, foot length 19 cm. Pulse rate 96 times per minutes regular; with respiratory rate was 31 times per minutes regular and axilla temperature $36,3^{\circ}\text{C}$.

Microcephaly with head circumference 34 cm (<P-3 (P-10.05)) head circumference

for age), anterior fontanel was closed, yellowish hair, firm, hard to leave. No flag sign. Forehead folds normal, with dysmorphic face. A "bird-headed" profile with receding forehead, large eyes, break like protrusion of the nose, narrow face, receding lower jaw, micrognathia was observed (Figure 1).

No pale conjunctiva, no icteric sclera, no sunken eyes, no edema palpebra, cleft eye was normal. A pupil reflex was normal, round pupil 3 mm diameter. Doll's eye movement, nystagmus aorstrabismus was not found. The ear, nose, and throat as well as neck examination were within normal limit. There were no palpable lymph nodes or nuchal rigidity. The chest

and abdomen examination were within normal limit.. The examination of upper and lower extremities showed no deformities. Physiological reflex were normal, there was no pathologic reflex found. There was no edema, no cyanosis. The physiological reflexes of the patella and Achilles tendon were normal. Motor strength of the four extremities was normal.

Complete blood count revealed white blood cell was 22.7 K/uL, haemoglobin was 10.3 g/dL, hematocrit 31.2 %, platelets count 788 K/uL. Liver function test revealed total bilirubin 0.26 mg/dL. indirect bilirubin 0.19 mg/dL. direct bilirubin 0.07, alkaline phosphatase 154 IU/L, SGOT 34

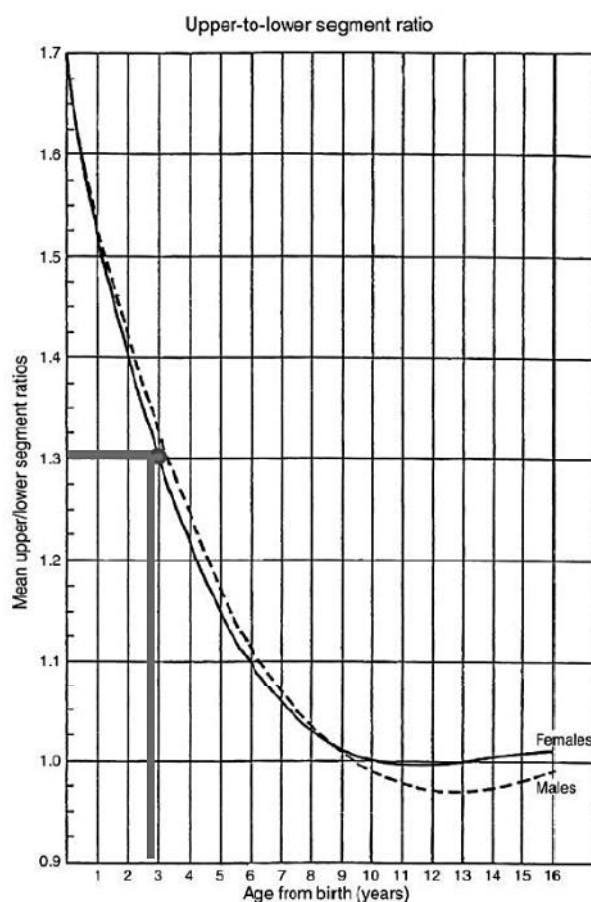


Figure 2. U/L ratio according to age.⁶



Figure 3. Bone age, epiphyseal plate on proximal, distal humerus and femur were appropriate for 6 months child.

IU/L, SGPT 12 IU/L, gamma GT: 10 IU/L, total protein 7.60 g/dL, albumin: 4.7 g/dL, globulin: 2.9 g/dL. Renal function test revealed blood urea nitrogen was 13.9 mg/dL and serum creatinine was 0.36 mg/dL, with glomerular filtration rate 84.02%. Glucose serum was 103.1 mg/dL, thyroid function test was FT4: 14.24 pmol/L and TSH: 2.68 pmol/L. Blood gas analysis revealed pH 7.36, pCO₂ 37 mmHg, pO₂ 35 mmHg, HCO₃⁻ 20 mmol/L, base excess: -4.1 mmol/L. Electrolyte serum revealed sodium 134 mmol/L, potassium 4.22 mmol/L,

chloride 106.9 mmol/L, calcium 11.2 mmol/L. Insuline-like growth factor 1 (IGF-1) was 57 ug/L. Liver function test, renal function test, glucose serum, thyroid function test, blood gas analyses, electrolyte serum and IGF-1 were within normal limit.

Imaging study (**Figure 3**), bone survey revealed that the bones pattern was appropriate for 6 months of age. Echocardiography resulted a normal intracardia with normal ventricular ejection fraction (EF 77%) and head CT-scan showed no abnormal brain parenchymal

was observed. Mantoux test also showed no induration (0 mm) and hyperemia. A chromosome analysis revealed 46,XX and there was no major structural abnormality (**Figure 4**).

Some consultations to other department were made to find if there were other abnormality to establish the diagnosis. Ophthalmology ward, pediatric neurology, and ear, nose, and throat (ENT) ward did not find any abnormality. Pediatric respiratory can't distinguish chronic disorder in lung.

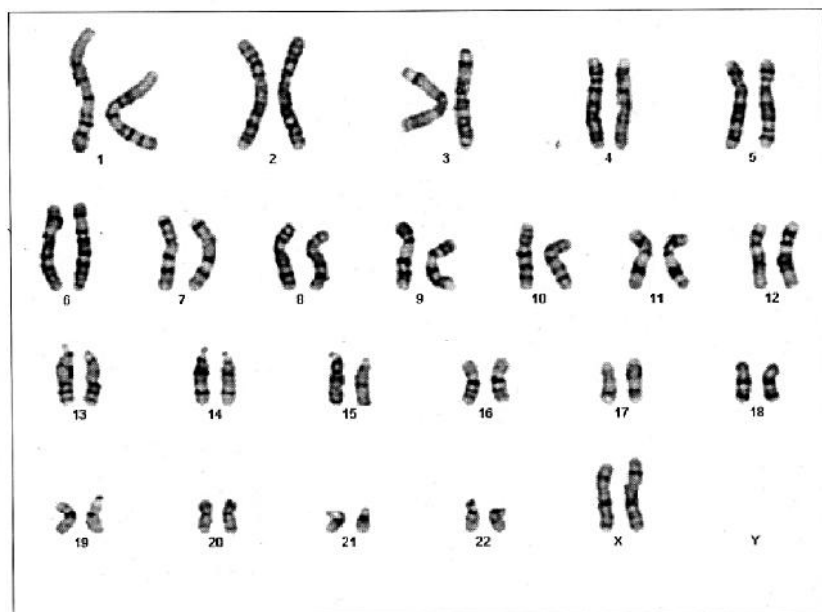


Figure 4. Chromosome analyses revealed no major structure abnormality.

Based on the clinical manifestation, imaging finding, and laboratory results, we assess the patient as Seckel syndrome. There was no specific treatments has been applied for patient other than education for the family and patient about this syndrome. Patient was hospitalized to establish diagnosis and was discharged after ten days of hospitalization.

DISCUSSION

Seckel syndrome also known with Harper's syndrome, Seckel's bird head syndrome, Seckel's nanism, Virchow-Seckel syndrome, SCKL, Bird-headed dwarfism, Seckel-type dwarfism, Nanocephalic dwarfism or Microcephalic primordial dwarfism I or SCKL.¹In 2000, a gene for Seckel syndrome was mapped to human chromosome 3q22.1-q24 (SCKL1) by homozygosity mapping in two

inbred Pakistanese families from the same village, with a genetic interval of 12 cM defined by loci D3S1316 and D3S3710. This gene has subsequently been identified as *ATR* (Ataxia-Telangiectasia and Rad-3 related protein) in the same families that affect splicing efficiency, resulting in low levels of *ATR* in affected individuals.⁷

Ataxia-Telangiectasia and Rad-3 related protein is essential, not only for development but also for somatic cell growth. The role of the *ATR* gene in DNA-damage response can explain the chromosomal instability in some Seckel patients. Another loci has been mapped in 2001 and in 2003 to chromosome 18p11.31-q11.2 (SCKL2) in one inbred Iraqi family and to chromosome 14q23 (SCKL3) in 13 Turkish families. These linkage results support the view that Seckel syndrome is a genetically heterogeneous condition and these genes

remain to be identified. Analysis of Seckel syndrome cell lines suggests that defects in *ATR* signaling are common, although the defective gene is not always *ATR*, suggesting a common pathway. A recent study suggested that SCKL3 is the predominant Seckel locus, but these results remain to be confirmed in other studies.^{7,8}

Seckel syndrome is an association of proportionate dwarfism of prenatal onset with characteristic dysmorphic features including severe microcephaly and a bird-headed like appearance, mental retardation and autosomal recessive inheritance. Seckel syndrome is characterized by intrauterine growth retardation (average birth weight 1540 g), severe proportionately short stature with severe microcephaly (mean post natal growth retardation is -7 SD with a range from -5 to -13 SD, a "bird-headed" profile with receding forehead, large eyes, break like protrusion of the nose, narrow face, receding lower jaw, micrognathia, and mental retardation (half of the patients have an IQ less than 50). Other occasional features of Seckel syndrome are premature closure of cranial sutures secondary to diminished brain growth, large eyes, antimongoloid slant of palpebral fissures, highly arched palate, cleft palate, dysplastic ears, clinodactyly of the 5th fingers, cryptorchidism, clitoridomegaly, hirsutism, crowded teeth with malocclusion, enamel hypoplasia, agenesis of the corpus callosum, pachygyria. Immunodeficiency and

significant predisposition to cancers have not been reported to date in Seckel Syndrome.^{1-3,9}

In our case, we found intrauterine growth restriction with birth weight and height was 1100 grams and 25 cm respectively at birth. Physical examination revealed severe proportionately short stature. A “bird-headed” profile with receding forehead, large eyes, breaks like protrusion of the nose, narrow face, receding lower jaw and micrognathia.

Diagnosis depends upon recognition of clinical findings in most cases. In some cases, increased chromosomal breakage has been reported, but it does not confirmed in all cases of Seckel Syndrome and cannot be used as a tool for the diagnosis.³ X-ray features include retarded bone age, frequent hip dysplasia and dislocation of the head of the radius. Definitive diagnosis acquires gen analyses to find SCKL 1, SCKL 2, and SCKL 3.⁸In our case, bone survey revealed retarded bone age which was appropriate for 6 months of age. Chromosome analysis revealed 46,XX with no major structural abnormality. Diagnosis was established with clinical, supported with x-ray features, as most Seckel syndrome cases. Gene analysis was not performed due to the unavailability of support tools.

Differential diagnoses most notably are microcephalic osteodysplastic dwarfism type II and type III, and microcephalic osteodysplastic dysplasia. It has been argued that type I and III represent phenotypic variability within

the same type of osteodysplastic primordial dwarfism. Type II microcephalic osteodysplastic dwarfism has been delineated as a separate entity, mainly relying on radiographic features with main features are short limbs with preferential distal involvement, coxa vara, epiphysiolysis and metaphyseal flaring with V-shaped distal femoral metaphyses. A complete radiological survey in the first year of life is necessary to make the distinction between Seckel syndrome and type II microcephalic osteodysplastic dwarfism.⁹In this case, main features of type II microcephalic osteodysplastic dwarfism were not revealed on bone survey.

No specific treatment was applied other than strong education for the family and patient itself about this syndrome, as they has passed difficult times of social isolation. Patient with Seckel may survive for a long time thou with mental retardation and physical limitation. Death in Seckel syndrome most are caused by other cardiovascular, hematological (acute myeloblastic leukemia (AML)), endocrinological, musculoskeletal and central nervous system diseases.^{5,9}In this case, we educated family about disease and further complications that might appear in future. There was no other systems disorder have been found and no specific medication has been given.

SUMMARY

A -2 year old female with intrauterine growth restriction, severe proportionately short

stature, a “bird-headed” profile with receding forehead, large eyes, breaks like protrusion of the nose, narrow face, receding lower jaw and micrognathia and from imaging study we found a retarded bone age on bone survey which bones pattern are appropriate for 6 months of age. Based on anamnesis, physical and laboratory examination, the patient was diagnosed with syndrome Seckel. We educated family about disease and further complications that might appear in future. There was no other systems disorder have been found and no specific medication has been given.

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