The Turkish Journal of Pediatrics 36: 239-242 1994

AASE–SMITH SYNDROME: REPORT OF A NEW CASE WITH UNUSUAL FEATURES*

*Sevgi Yetgin MD**, Sevim Balcı MD***, Gülersu İrken MD****
*Turgay Coşkun MD*****, Burhan Say MD******

SUMMARY: Yetgin S, Balcı S, İrken G, Coşkun T, Say B. (Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Aase-Smith syndrome: report of a new case with unusual features. Turk J Pediatr 1994; 36: 239-242.

A new case of Aase-Smith syndrome has ben reported with additional findings, including microcephaly, axial rotation of the kidneys, preaxial polydactyly and leukopenia. The, patient had almost complete clinical remission with corticosteroid treatment. The findings in this case suggest that it is very difficult to differentiate Aase-Smith syndrome from Blackfan-Diamond and Fanconi's anemias as well as from those cases reported by Murphy and Lubin, and Jones and Thompson. *Key words: Aase-Smith syndrome, Blackfan-Diamond anemia, Fanconi's anemia.*

In 1969 the association of congenital hypoplastic anemia (CHA) and triphalangeal thumbs was described by Aase and Smith as an entity different from both Fanconi pancytopenia and the radial aplasia-thrombocytopenia (TAR) syndrome[1].

The purpose of this report is to present another case who also had unusual findings including microcephaly, axial rotation of the kidneys, preaxial polydactyly, leukopenia and chronic steatorrhea. An almost complete clinical remission upon corticosteroid treatment was observed.

Case Report

A 15-month-old female infant was seen because of pallor and growth retardation. The history showed that she was the second child born to a couple who were first cousins. The delivery was by breech presentation at term, but the baby was small for gestational age. At birth, a preaxial polydactyly of the right hand was noted. Soon after birth the infant was put on a diet of cow's milk. She had chronic steatorrhea and recurrent bronchopneumonia. At the age of 24 days, the anemia was severe enough to require a blood transfusion. There was no family history of

* From the Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara.
** Professor of Pediatrics and Pediatric Hematologist, Hacettepe University Faculty of Medicine.
*** Professor of Pediatrics and Geneticist, Hacettepe University Faculty of Medicine.
**** Associate Professor of Pediatrics and Pediatric Hematologist, Dokuz Eylül University Faculty of Medicine, İzmir.
***** Associate Professor of Pediatrics, Hacettepe University Faculty of Medicine.
****** Professor of Pediatrics and Geneticist, H. Allen Chapman Research Institute of Medical Genetics, Tulsa, Oklohoma.

hematological disease or congenital anomalies, except that the mother had a white forelock but normal auditory function. The patient's six-year-old brother was in good health. The patient had growth retardation, with a height of 68 cm, weight 5700 g, and head circumference 43 cm all being below the 3rd percentile. She also had micrognathia, a short neck, a strawberry hemangioma 2 cm in diameter on the left scapula, and bilateral proximally located triphalangeal thumbs (Fig. 1).

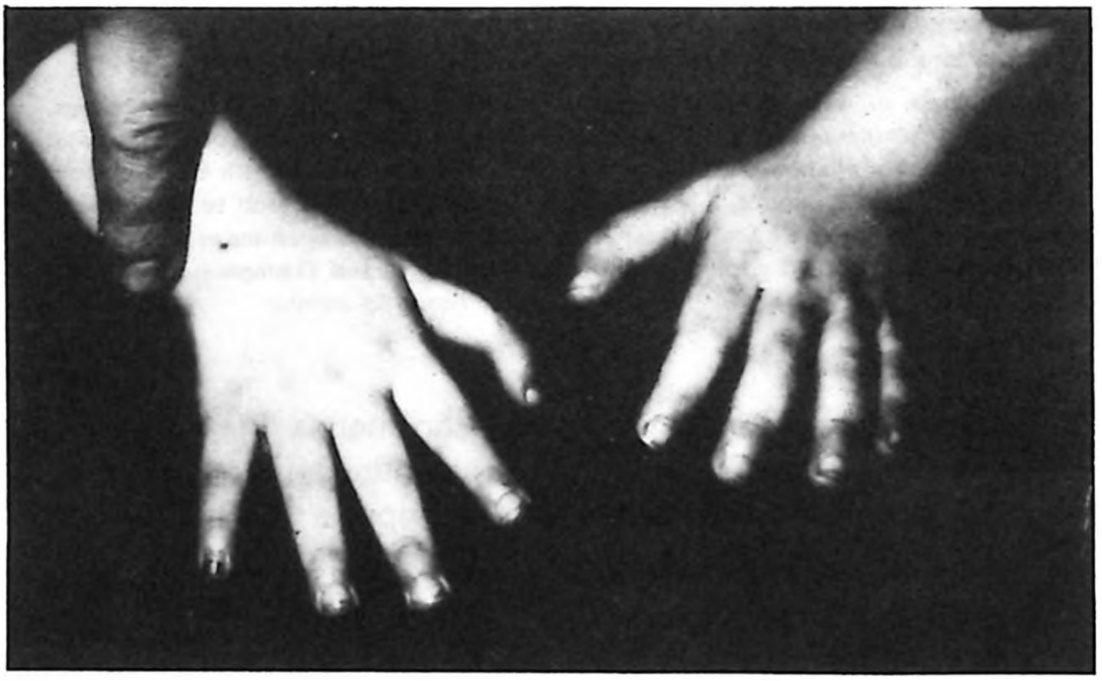

Fig. 1: Bilateral triphalangeal thumbs.

Hemoglobin was 4.87 g/dl, and white cell count was 2.8×10^9/L with 48% neutrophils, 50% lymphocytes and 2% monocytes. Reticulocyte count was 3% mean corpuscular volume (MCV) 99 fl and platelets 320×10^9/L. Red blood cells showed mild hypochromia. Bone marrow displayed normal cellularity with megaloblastoid changes, occasional fatty spaces, and increased mast cells. Chromosome analysis on cultured lymphocytes exhibited normal 46, XX karyotype. Sister chromatid exchange (SCE) and diepoxybutane (DEB) test were also normal.

Levels of serum iron and total iron-binding capacity were 11.2 and 63 µmol/L, respectively. Folic acid level was 1.9 µg/L; vit B_{12} 600 ng/L Mg 1.76 mg/dl; Zn 35 µg/dl. Total protein was 6 g/dl and albumin 3.7 g/dl. glucose-6-phosphate-dehydrogenase activity, acid ham, sugar-water test, C_3, C_4 and growth hormone levels were all within the normal limits. Duodenal fluid tryptic activity was normal, and direct Coombs tests were negative. Sweat chloride was found to be increased on four separate measurements: 61, 95, 53 and 63 mEq/L (upper normal limit 45 mEq/L). Radiologic studies showed bilateral triphalangeal thumbs and hypoplasia of carpal bones. There was axial rotation of the kidneys,

specifically over the lower pole of the left kidney, suggesting horseshoe kidney malformation. The connection was a fibrous band.

The patient was treated with iron, folic acid, multivitamins, zinc and pancreatic enzymes as well as a diet enriched with medium-chain fatty acids due to the presumptive diagnosis of cystic fibrosis. There was no satisfactory response to this therapeutic regimen. The restricted diet was discontinued, but blood transfusions were administered for three years at 3-4 month intervals. At the age of 4.5 years, the diagnostic possibility of Aase-Smith syndrome was raised on the basis of congenital hypoplastic anemia and triphalangeal thumb associated with normal SCE, DEB test and chromosomal analysis. Corticosteroid treatment (2 mg/kg po) was started, after which a significant response in Hb level (12.5 g/dl) was noted but not in WBC ($3x10^9$/L) within two months. Corticosteroid therapy was tapered to 1 mg/kg and continued for the next two months and then tapered again for one year at 5 mg daily doses. Subsequent examination revealed improved physical growth (height 93 cm, weight 15 kg), and the findings such as diarrhea and lower respiratory tract infections had more or less disappeared. Thus, the earlier findings suggestive of cystic fibrosis were considered to have been no more than a reaction to cow's milk, responding as expected to steroid therapy.

At last follow-up, the patient was 7.5 years old, 102 cm in height and 17.5 kg in weight, with a head circumference of 49 cm all below the 3rd percentile. Hemoglobin levels were consistently in the range of 10-12 g/dl. Macrocytosis had completely disappeared, but WBC counts showed no significant changes ($2\text{-}3.9x10^9$/L).

Discussion

To the best of our knowledge, only ten well-documented cases of Aase-Smith syndrome have been reported in the literature since 1969[1-11] although two other probable cases have been documented[12-13]. Our patient had characteristic findings of the syndrome, such as CHA, triphalangeal thumbs and normal SCE and chromosomal analysis. Additionally, she had short stature, a short neck, microcephaly, proximal polydactyly, urinary system abnormality and decreased WBC count, which would suggest the diagnosis of Fanconi's anemia. None of the reported patients with Aase-Smith syndrome have had similar findings. The mother's having a white forelock but normal hearing also pointed to the possibility of Fanconi's anemia. Fanconi's anemia heterozygotes are known to have some increased skin pigmentation and findings similar to those mentioned above. A few other patients are on record with multiple physical abnormalities and leukothrombocytopenia, suggesting Fanconi's anemia[2,3]. While our patient had persistent leukopenia, the normal cytogenetic findings and early onset of anemia seem to exclude Fanconi's anemia as a diagnostic possibility. Also, such a good response

to corticosteroid treatment is not usually expected in Fanconi's anemia cases, giving further support to the diagnosis of Aase-Smith syndrome.

In patients with CHA as well as Aase-Smith syndrome, recovery has been obtained by administration of corticosteroids in most cases. Spontaneous remission has also occurred in both groups of patients. Although triphalangeal thumbs is one of the cardinal findings of Aase-Smith syndrome, in 1978 Alter pointed out that triphalangeal thumbs occurred in 6 of 133 cases of CHA[14]. In 45 of these cases (34%), there was some type of hand abnormality. For that reason, Alter suggested that this syndrome is not an entity distinct from the Blackfan-Diamond syndrome[12]. It is clearly very difficult to differentiate with certainty Aase-Smith syndrome from Blackfan-Diamond and Fanconi syndromes as well as from entities described by Murphy and Lubin[2], and Jones and Thompson[3]. The etiology of Aase-Smith syndrome is still unknown; however, the occurrence in siblings and in both sexes makes autosomal recessive inheritance most likely. We believe further cases need to be studied to resolve these questions.

REFERENCES

1. Aase JM, Smith DW. Congenital anemia and triphalangeal thumbs: a new syndrome. J Pediatr 1969; 74: 471-4.
2. Murphy SH, Lubin B. Triphalangeal thumbs and congenital erythroid hypoplasia: report of a case with unusual features. J Pediatr 1972; 81: 987-9.
3. Jones B, Thomson H. Triphalangeal thumbs associated with hypoplastic anemia. Pediatrics 1973; 52: 609-12.
4. Terheggen HG. Hypoplastische anamie mit dreigliedrigem daumen. Z. Kunderheilkd 1974; 118: 71-80.
5. van Weel-Sipman M, van de Kamp JJP, de Koning JA. Female patient with "Aase syndrome". J Pediatr 1977; 91: 753-5.
6. Higginbottom MC, Jones KL, Kung FH, Koch TK, Boyer JL. The Aase syndrome in a female infant. J Med Genet 1978; 15: 484-6.
7. Pfeiffer RA, Ambs E. Das Aase-syndrome: autosomal-rezessiv vererbte, konnatal insuffiziente Erythropoese und Triphalangie der Daumen. Monatsschr Kinderheilkd 1983; 131: 235-7.
8. Muis N, Beemer FA, van Dijken P, Klep-de Pater JM. The Aase syndrome. Case report and review of the literature. Eur J Pediatr 1986; 145: 153-7.
9. D'Avanzo M, Pistoia V, Tolone C, Toraldo R, Santinelli R, Lafusco F. Aase-Smith Syndrome: report of a new case. Br J Haematol 1988; 70: 125-6.
10. McKusick VA: Mendelian Inheritance in Man. Catolog of Autosomal Dominant, Autosomal Recessive, and X-linked Phenotypes. (9th ed). Baltimore: Johns Hopkins University Press; 1990: 1031.
11. Jones KL. Smith's Recognizable Patterns of Human Malformation (4th ed). Philadelphia: WB Saunders Co; 1988: 277.
12. Diamond LK, Allen DM, Magill FB. Congenital (erythroid) hypoplastic anemia. A 25-year study. Am J Dis Child 1961; 102: 403-15.
13. Harvey DR. Congenital hypoplastic anemia. Proc R Soc Med 1966; 59: 490-1.
14. Alter BP. Thumbs and anemia. Pediatrics 1978; 62: 613-4.