HAND - FOOT SYNDROME IN SICKLE CELL DISEASE

İzzet Berkel, M. D.,* Şinasi Özsoylu, M. D.*

and Behice Çorbacioğlu, M. D.**

Sickle cell anemia is the most common hemoglobinopathy encountered in Turkey and almost exclusively seen in Eti Turks in whom other abnormal hemoglobins are also prevalent.[1,2] Aksoy reported that the frequency of hemoglobin S in Eti Turks is around 16.8 per cent.[3]

Clinical signs and symptoms of sickle cell anemia are variable. The symptoms in a child under one year of age may differ from those seen in older children, and the diagnosis is usually difficult under three months of age because of high fetal hemoglobin in the red cells. Symptoms such as pallor, fever, pain in various areas of the body may develop, but painful swelling of the dorsa of hands and feet, either separately or together, so called the hand - foot syndrome, may be the earliest clinical manifestation.[4]

From the opening of Hacettepe Children's Hospital in 1958 to July 1966, 26 cases of sickle cell anemia in children under 16 years of age were seen in the hematology department.

In this paper the cases of six patients with sickle cell anemia, in whom diagnosis was made because of typical signs of the hand - foot syndrome will be presented. Although this syndrome is not rare in patients with sickle cell disease, its importance as one of the earliest signs of sickle cell anemia in infancy is often overlooked by the practicing physician. The purpose of this report is to call attention to this manifestation, which although it has been observed in the Eti Turks in Southern Anatolia, has nevertheless not been previously reported from Turkey.[5]

Case Reports

Case 1. S. A., a 21 month old white male of Eti Turk extraction, was brought to the hematology clinic with complaints of pallor, anorexia, fatigue

From Ankara University Hacettepe Faculty of Medicine, Hacettepe Children's Hospital, Ankara.

* Assistant Professor of Pediatrics, Hematologist.

** Associate in Pediatrics, Fellow in Hematology.

and occasional swelling of the hands and feet. No symptoms were noted until six months of age when he developed fever, pallor, anorexia and painful swelling, first of the hands and later of the feet, which lasted for about a week. He seemed to feel pain in his extremeties, and a swelling of the right thigh and femur developed which subsided in a few days. There had been a history of similar episodes involving hands and feet on many occasions. A marked pallor was also noted. His development was within normal limits and his history was not otherwise contributory. Of his siblings, an eight year old male and two females of five and three years were said to be healthy; a male sibling had died at 18 months of age of an unknown disease. It was said that he also had been very pale. Both parents seemed in good health.

Physical examination revealed a thin, moderately pale, chronically ill-appearing boy. His weight was 9.9 kg and his temperature was 37° C. Spleen was palpable at the left costal margin. Fingers and dorsa of both hands were swollen and painful to the touch. There was no pitting. The rest of the physical examination was within normal limits. Laboratory findings are summarized in the table. Hemoglobin electrophoresis in the patient showed a component which moved with hemoglobin S. Both mother and father had components which moved with hemoglobin A and S. An x-ray of the hands on admission showed a soft tissue swelling in the phalanges. There was no periosteal thickening or osteolytic changes (Figure 1). Since the patient returned to his town, no follow up films were taken.

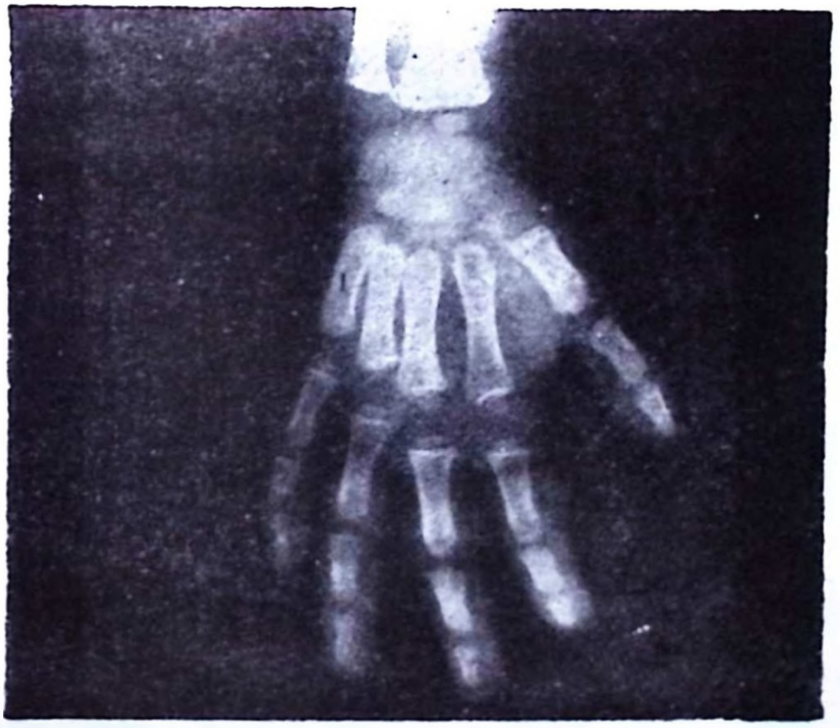

Figure 1. X-ray of the hands showing soft tissue swelling in the phalanges (Case 1).

Case 2. Ü. D., a 12 month old white girl of Eti Turk extraction, was admitted to the hospital with complaints of pallor, diarrhea, fever and swelling in both hands and feet. At the age of three months, she had developed fever and pallor, and the dorsal aspect of both hands and feet had been swollen and tender. These swellings had lasted a week or more and had recurred several times before her admittance to Hacettepe. She was always very irritable, an-

orexic and feverish during these episodes. Her development was within normal limits, and a five year old brother was reported to be healthy.

Physical examination showed a pale and quiet female with a flat fontanel measuring 2x2 cm. Her weight was 8.3 kg, her height was 72 cm and temperature 37.5° rectally. Liver and spleen were palpable 3 cm and 2 cm respectively at the costal margins. Dorsa of the hands were edematous and tender and both feet were swollen. There were no other remarkable observations. Results of the laboratory examinations are listed in the table. Hemoglobin electrophoresis of the patient showed a hemoglobin pattern which migrated with S. Both parents had S and A bands. An x-ray of the extremities of the patient showed periosteal reaction in the fourth metacarpal bone of the left hand.

Case 3. S. Ö., an 18 month old white boy of Eti Turk extraction, was brought to the hematology clinic with complaints of pallor, fever, and swelling of hands and wrists. The parents noted a marked pallor in the child at about one year of age accompanied by irritability, anorexia, fever and recurrent swellings in fingers, wrists and both feet. Ten days prior to admission, his fingers again became swollen and painful and he was treated by a local physician with prednisolone for a week. Two siblings and the parents were said to be healthy.

Physical examination. He was markedly pale with tender swellings in both hands and feet. Pharynx was hyperemic and beta hemolytic streptococci were cultured from the throat. The liver and spleen were enlarged 4 cm and 2.5 cm at the respective costal margins. His hematologic findings are tabulated in the table. His hemoglobin electrophoresis showed an SS pattern and both parents had the hemoglobin S trait. Radiological examination of hands and feet disclosed periosteal reaction and new bone formations in the first, and fifth metacarpals and in the first phalanx of the middle finger of the right hand. Similar changes were observed in the second and third metacarpals of the left hand.

Case 4. S. S., an 18 month old white male of Eti Turk extraction, was admitted to the hospital because of pallor and swelling of hands and feet which first started a year before and which had recurred many times. He developed normally until two months of age, at which time his pallor progressively increased and he showed frequent temperature elevations. The father was 28 years old and in good health. The mother had died of puerperal infection. Three brothers of the patient had died at the ages of three, one and a half years and at six months of a similar illness characterized by pallor and swelling in the extremities and abdomen.

Physical examination showed a very pale malnourished infant with a flat fontanel measuring 1x1 cm. His weight was 5.35 kg and height 65 cm. His temperature was 37°C rectally. Both hands and feet were swollen and tender on touch. Spleen was palpable at the left costal margin. Laboratory findings are summarized in the table. Hemoglobin electrophoresis showed an SS pattern. His father had hemoglobin S trait. Radiological examination of the left hand (Figure 2) showed periosteal reaction and new bone formations in the first, second, third and fourth metacarpals. There were also focal areas of bone destruction with edema of the soft tissue. The right hand (Figure 3) showed similar changes in the first, second, fourth and fifth metacarpals. The right radius

TABLE 1

	Hemoglobin (gm/100ml)	WBC/mm³	Peripheral smear	Reticulocyte count (%)	Fetal Hemoglobin (%)*	Hemoglobin electrophoresis**	Serum bilirubin mg/100 ml †
Case 1 - E. A.	7.85	7.800	marked hypochromia, anisocytosis, moderate polychromasia, rare target cells	7.0	3.2	SS	Total 1.1 direct 0.3
Case 2 - Ü. D.	6.22	10.000	moderate hypochromia, anisocytosis, poikilocytosis, polychromasia, rare target cells	8.0	5.2	SS	—
Case 3 - S. Ö.	8.90	18.500	moderate hypochromia, anisocytosis, poikilocytosis, polychromasia, rare target cells	13.8	24	SS	—
Case 4 - S. S.	6.15	17.400	marked hypochromia, anisocytosis, poikilocytosis, rare target cells and sickle cells, moderate polychromasia	3.0	4.5	SS	Total 0.6 direct 0.1
Case 5 - E. T.	7.70	13.400	marked hypochromia, anisocytosis and polychromasia, rare target cells	0.2	11	SS	—
Case 6 - V. T.	2.80	11.500	marked hypochromia and polychromasia, marked anisocytosis, many target cells	6.2	4	SS	Total 2.7 direct 0.6

* Determined by the Singer method.[10]

** Filter paper electrophoresis was done using Jouane apparatus, veronal buffer, Ph 8.6 ionic strength 0.05.

† Determined by the Van den Bergh method.[11] For other hematological tests, conventional methods were used.[12]

and ulna also had some periosteal reaction. A similar periosteal reaction was also present in the first, third and fourth metatarsals of the left foot accompanied by some soft tissue swelling (Figure 4).

Case 5. E. T., a two year old white male of Eti Turk extraction, was brought to the Hematology Clinic with marked pallor, fatigue and fever. These symptoms were first noted by the parents a year previous to admission. There was also a history of swelling and pain in his legs starting a few months before which had lasted for two weeks and had been treated with prednisolone. The parents were first cousins and were healthy. Two male siblings had died of conditions unknown to the parents at 18 and 13 months. They had both appeared to the parents to have been very pale.

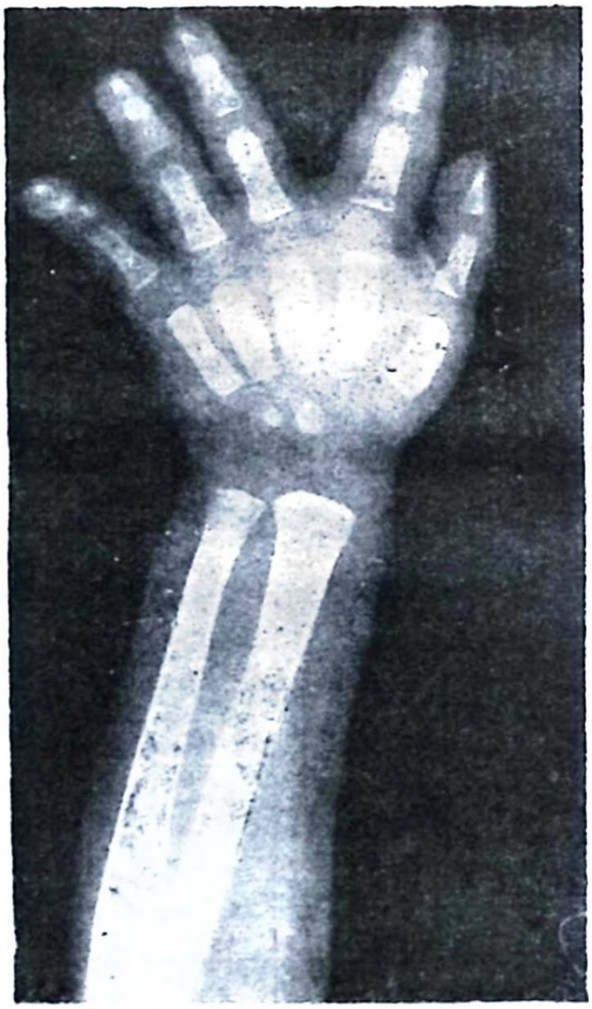

Figure 2. X-ray of the left hand shows periosteal reaction and new bone formations (Case 4).

Physical examination revealed a pale boy with slightly puffy eyelids. Liver and spleen were 3 cm enlarged at their respective costal margins. Both hands were swollen and tender without pitting edema the fingers were fusiform in appearance. Hemoglobin electrophoresis showed an SS pattern. The parents had S hemoglobin trait. Radiological examination of the hands was not done.

Case 6. V. T., a four year old white male of Eti Turk extraction, was admitted to the hospital with symptoms including pallor, anorexia and a protuberant abdomen. At about one year pallor had developed and frequent epi-

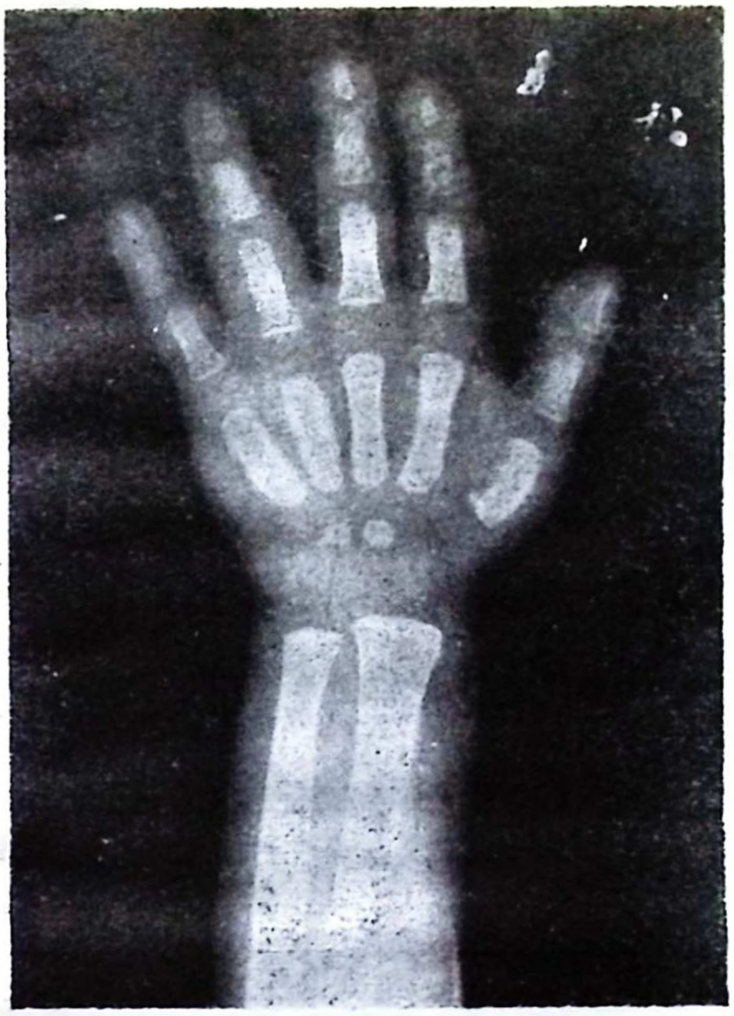

Figure 3. X-ray of the right hand showing new bone formations (case 4).

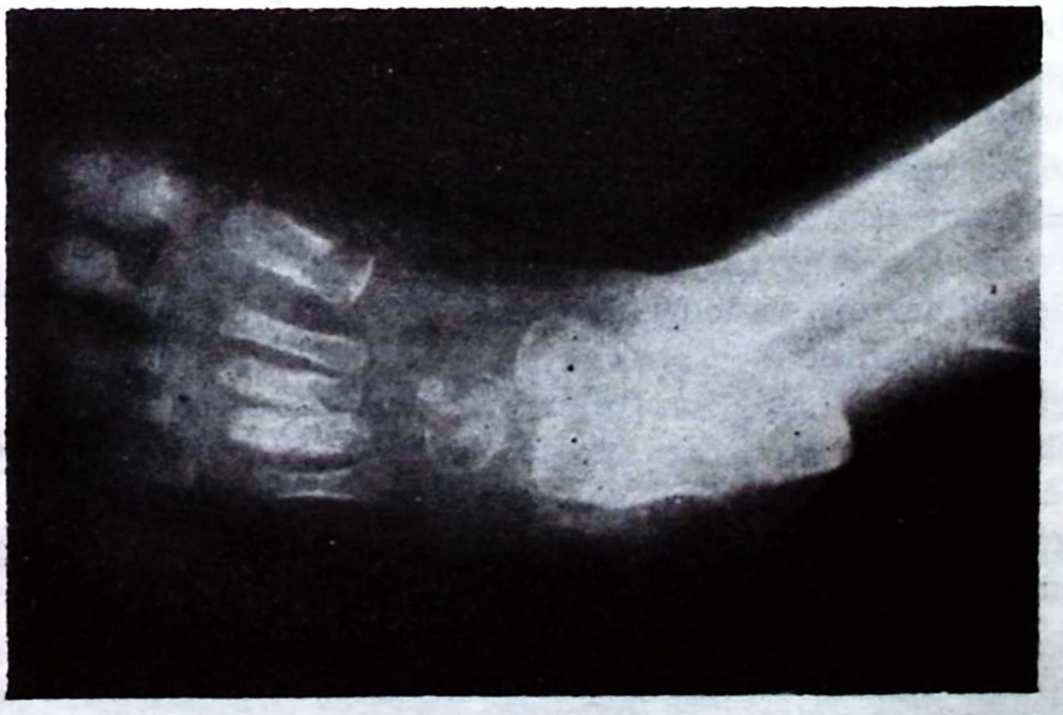

Figure 4. X-ray of the left foot (case 4).

sodes of fever were noted. He had also suffered from bronchopneumonia two years before admission. His parents noticed that his abdomen became progressively enlarged after one year of age. There were recurrent painful swellings in both hands and feet which lasted for periods of 10-15 days. Both parents were said to be healthy. Siblings of nine years, six years and eight months were also in good health.

Physical examination showed a very pale child with both hands edematous and tender. The fingers were fusiform in shape. The liver was enlarged 3.5 cm and the spleen 4 cm. At the apex a grade II/IV systolic murmur was heard. Hematological findings are listed in the table. His hemoglobin on electrophoresis showed the SS pattern, while his parents had HbS trait. Radiological examination of the hands showed soft tissue swelling on both sides. The second and the fifth metacarpals of the left hand had periosteal reaction with some new bone formation (Figure 5).

Discussion

Symptoms of sickle cell anemia may usually not be seen in infants under three months of age.[6, 7] The symptoms which appear after this age are pallor, fever, splenomegaly and swelling of hands and feet which increase in frequency and degree. After six months other symptoms usually seen are hepatomegaly, frequent infections, irritability and colic, abdominal distention, jaundice, heart murmur, nausea and vomiting, cardiomegaly, etc.[7, 8] Hand-foot syndrome may be the earliest manifestation of sickle cell disease in infants under one year of age. One of the earliest cases was reported by Ivy and Howard in a one year old negro girl who had swelling and tenderness in both hands which lasted for 22 days.[9] Since the publication of this case in 1953 many case reports on this subject have been published. By 1963, 52 cases of the hand-foot syndrome had been reported in the literature according to Watson et al.[4] They also presented 20 cases histories, in 14 of which the condition had been diagnosed before the age of two. None of the patients were over seven years. Booker et al[7] found that 6 (33 %) out of 18 patients who had sickle cell anemia at under two years first showed symptoms of the hand-foot syndrome before the age of two. Nine of these 18 patients had swelling in hands or feet either once or on repeated occasions during the first two years of life. Porter and Thurman[8] analyzed 37 females and 27 males with sickle cell anemia whose cases had been diagnosed before they reached 12 months of age. Although the incidence of this syndrome was 37 per cent, only 19 per cent had positive x-rays. Lambotte[13] states that he has seen the hand-foot syndrome in 80 per cent of 1200 cases of sickle cell anemia in African infants in the Congo. The ages of 26 patients

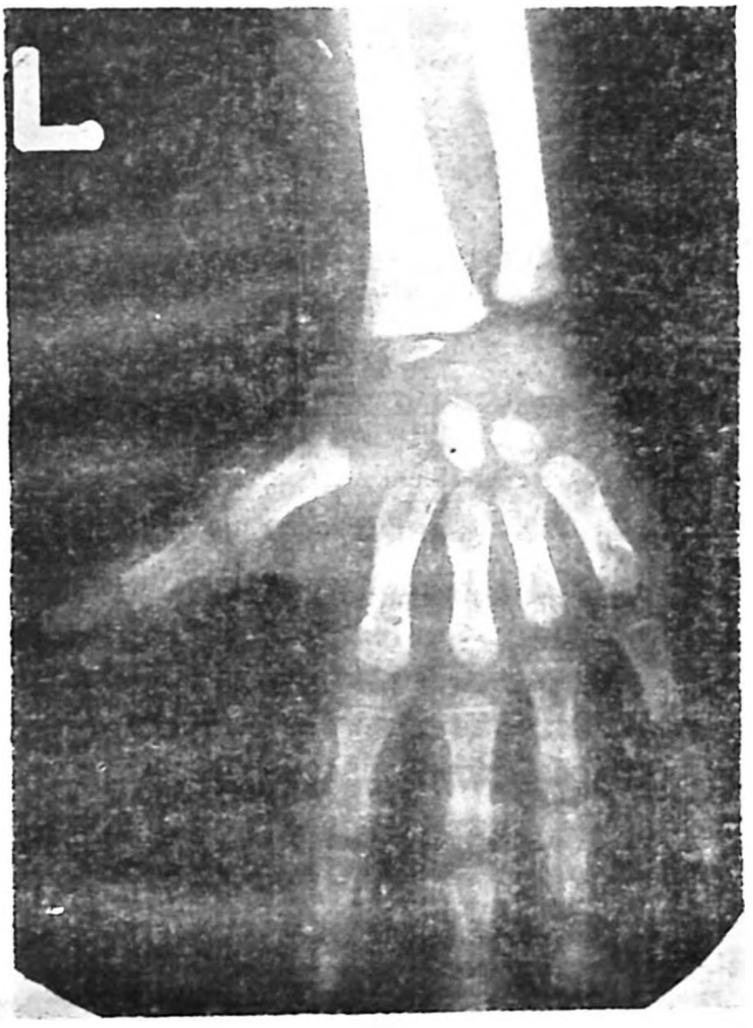

Figure 5. Second and fifth metacarpals of the left hand showing periosteal reaction and new bone formation (case 6).

with sickle cell anemia seen in our hematology clinic were between 11 months and 14 years. There were 18 males and 8 females. Six out of the 26 had typical signs and findings of the hand-foot syndrome and five others had similar complaints in their histories. This number may be increased since characteristics of this sign had not been specifically asked for in histories taken prior to 1960. Thus the true incidence in our series may be higher than 42.3 per cent. With the exception of a four year old boy, all of the patients were under two. Our small series confirmed the observation that the hand-foot syndrome is not seen in patients over seven years of age.[17, 13] After the age of two years, the long bones are more often affected.

In the hand-foot syndrome the swelling is symmetrical and involves the fingers, toes and dorsal aspects of the hands and feet. Edema is of the nonpitting type. Usually hands are more frequently affected than feet. The episodes are often associated with infections and characterized by swelling and pain in the affected areas. The

pain may be severe during the first few days and the swelling may last from one to three weeks, and recur several times in the same patient.

Exposure of the extremities to cold may be a precipitating factor, but this has not been found true in all cases.[4] Stasis and ischemic infarction due to sickling of the red cells in the capillary beds in the bones of the hands and feet is responsible for pain and edema. In the hand-foot syndrome the metacarpals, metatarsals and phalanges are infarcted by multiple small capillary blocks. Radiological examination may not show any other changes than soft tissue swelling during the acute phase, but bony changes appear 7 to 10 days after the onset of the swelling in some cases.[4, 7, 14] These are usually seen as periosteal thickening and osteolytic changes in metacarpals, metatarsals and phalanges. The mildest change appears as a subperiosteal new bone formation. Some irregular radiolucent areas are also observed in the affected bone.[4, 14] These changes may be reversible but some cases may exhibit bony destruction.

Often it is difficult to make a differential diagnosis between the hand-foot syndrome and osteomyelitis. It is known that salmonella osteomyelitis does occur in sickle cell anemia,[16–18] but it is much less common than the hand-foot syndrome.[4] In our small series of 26, only one case of salmonella osteomyelitis was observed.[18] Apart from identification by positive cultures; unilateral involvement of the long bones may help in differentiating osteomyelitis from the hand-foot syndrome. Otherwise, radiological changes may be indistinguishable from those of osteomyelitis. Dactylitis or osteomyelitis caused by tuberculosis or syphilis can be eliminated by negative skin tests, negative serology and case histories themselves. Clinically rheumatoid arthritis may be suspected, but it is easily differentiated by appropriate tests. However in two instances, our patients had been diagnosed as having arthritis by local physicians and had been treated with corticosteroids.

Since episodes of symmetrical edema of the hands or feet accompanied by pain is fairly common among infants and toddlers with sickle cell anemia, when these symptoms are observed in an anemic child, sickle cell anemia should be one of the first diagnoses considered.

Summary

During the last eight years, 26 cases of sickle cell anemia have been seen in this hospital. Six patients manifested typical hand-foot

syndrome and five others had similar episodes in their histories. The hand-foot syndrome may be one of the earliest signs of sickle cell disease in infancy and every patient with this condition should be considered as having sickle cell anemia until it is proven otherwise.

REFERENCES

1. Aksoy, M.: Abnormal hemoglobins in Turkey. in Abnormal Hemoglobins-A Symposium, edited by Jonxis, and Delafresnaye, Springfield, Illinois, Charles C. Thomas, 1959, p. 216.
2. Say, B., Berkel, I and Yaşrın, N.: Türkiyede Sickle-cell anemisi problemi, Çocuk Sağlığı ve Hastalıkları Dergisi 4 : 129, 1961.
3. Aksoy, M.: Hemoglobin S in Eti-Turks and the Allewits in Lebanon. Blood 17: 657, 1961.
4. Watson, R. J., Burko, H., Megas, H. and Robinson, M: The hand-foot syndrome in sickle cell disease in young children, Pediatrics 31: 975, 1963.
5. Aksoy, M.: Personal communication, 1966.
6. Haggard, M. E. and Schneider, R. G.: Sickle cell anemia in the first two years of life, J. Pediat. 58 : 785, 1961.
7. Booker, C. R., Scott, R. B. and Ferguson, A. D.: Studies in sickle cell anemia XXII. Clinical manifestations of sickle cell anemia during the first two years of life, Clin. Ped. 3 : 111, 1964.
8. Porter, F. S. and Thurman, W. G.: Studies of sickle cell disease. Diagnosis in infancy, Am. J. Dis. Child. 106: 35, 1963.
9. Ivy, R. E. and Howard, F. H.: Sickle - cell anemia with unusual bone changes, J. Pediat. 43 : 312, 1953.
10. Singer, K., Chernoff, A. I. and Singer, L.: Studies on abnormal hemoglobins; their demonstration in sickle cell anemia and other hematologic disorders by means of alkali denaturation, Blood 6 : 413, 1951.
11. Fister, H. J.: Bilirubin method B. 10 P. I. Manual of Standard Procedures for Spect. Chem., Standard Scien. Supp. Corp. Pub., New York, 1950.
12. Cartwright, G. E.: Diagnostic Laboratory Hematology, Third Edition, New York, Grune and Stratton, 1963.
13. Lambotte, C.: Hand-foot syndrome in sickle-cell disease (Correspondence), Am. J. Dis. Child. 104: 200, 1062.
14. Trowell, H. C., Raper, A. B. and Welborn, H. F.: The natural history of homozygous sickle-cell anaemia in Central Africa, Quart. J. Med. 26 : 401, 1957.
15. Moseley, J. E.: Bone Changes in Hematologic Disorders (Roentgen Aspects), New York, Grune and Stratton, 1963, pp. 12-26.
16. Hook, E. W., Campbell, C. G., Weens, H. W. and Cooper, G. R.: Salmonella osteomyelitis in patients with sickle-cell anemia, New England J. Med. 257 : 403, 1957.
17. Roberts, A. R. and Hilburg, L. E.: Sickle cell disease with Salmonella osteomyelitis, J. Pediat. 52 : 170, 1958.
18. Aksoycan, N., Özsoylu, Ş. and Gülmezoğlu, E.: Salmonella Muenchen Osteomyelitis in a white boy with sickle cell disease, The Turkish J. Ped. 1: 162, 1958.