Acta Paediatrica Hungarica 31 (3), pp 279-289 (1991)

WHISTLING FACE SYNDROME
A case report and literature review

M.M. MILLNER[1], I.D. MUTZ[2], W. ROSENKRANZ[3]

Unit of Paediatric Neurology, Department of Paediatrics[1], Department of Paediatrics, Landeskrankenhaus Leoben, Austria[2], Department of Human Genetics, University of Graz[3]

Received 26 April 1990

The cranio-carpo-tarsal or "whistling face" syndrome was first described by Freeman and Sheldon in 1938. More than 60 cases with great variability of expression are known till now and autosomal dominant as well as recessive inheritance and sporadic cases suggest a genetic heterogeneity.

We review 60 well-documented cases of the literature and present a patient with a severe form, who died of bronchopneumonia at the age of 9 months. The facial stigmata of his mother and the ulnar deviations of his maternal grandfather support the autosomal inheritance of the syndrome.

INTRODUCTION

The cranio-carpo-tarsal syndrome or whistling face syndrome (WFS) first described by Freeman and Sheldon in 1938 is a disorder with great variability involving the face and the musculoskeletal system. We present a patient with a very severe form of this syndrome and review 60 cases of the literature.

CASE REPORT

A. S., a boy, was born after an uneventful pregnancy as the first child of non-consanguineous parents. His otherwise healthy mother has a small mouth, a high arched palate, and little mimicry. A photograph of the deceased maternal grandfather shows severe ulnar deviation of all fingers, which had been interpreted as sequelae of a "rheumatic disease" (Fig. 1).

Akadémiai Kiadó, Budapest

The child was delivered by cesarian section because of an abnormal cardiotocogramm. Birth weight was 2680 g, length 49 cm, head circumference 31.5 cm. The Apgar scores after 1, 5 and 10 minutes were 8,9, and 9, (respectively). The child was intubated and ventilated because of "poor respiration".

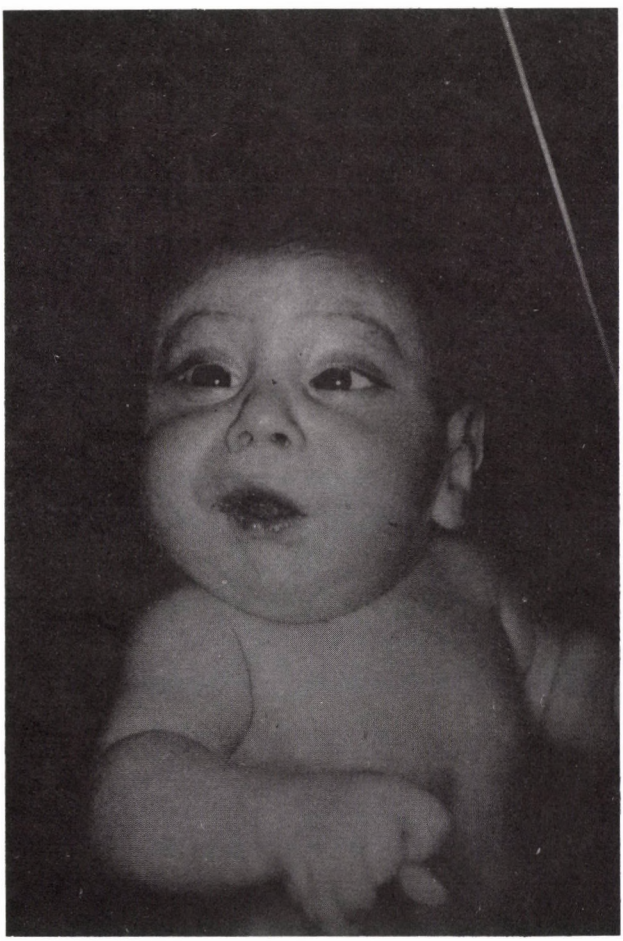

Fig. 1.

On examination at birth there were lack of mimicry, small and open mouth "pointed as for whistling", microcephaly with prominent supraorbital ridges and flat forehead, small anterior fontanel (<1) cm), ptosis of the eyelids, infrequent eye blink with missing blink reflex, and one row of long, straight and coarse eyelashes. His nose was small with plug-like nostrils, the philtrum long, the cheeks full but flabby, the mandible small, the large ears low set, and the neck short. The fingers were held in ulnar deviation and partial external rotation. The thumb and the fifth finger were flexed; the fingers could neither actively be bent nor flexed, which led to a pseudo-simian-crease. There were striking flexion contractures of the toes, lack of spontaneous movements and the stiffness of the skeletal muscles. The legs were adducted and internally rotated and the feet were in plantar flexion. The tendon reflexes were normal (Fig. 2).

Fig. 2.

Radiological examination revealed a steep fossa cerebri anterior (Fig. 3) but no other abnormalities. Ultrasound of the brain was normal, a cCT scan showed a moderately enlarged anterior part of the interhemispherical fissure and the pericerebellar space. Complete blood count, electrolytes, copper, and urine analysis were normal, no storage phenomena could be detected. Ophthalmoscopy revealed normal fundi and normal iris vasculature.

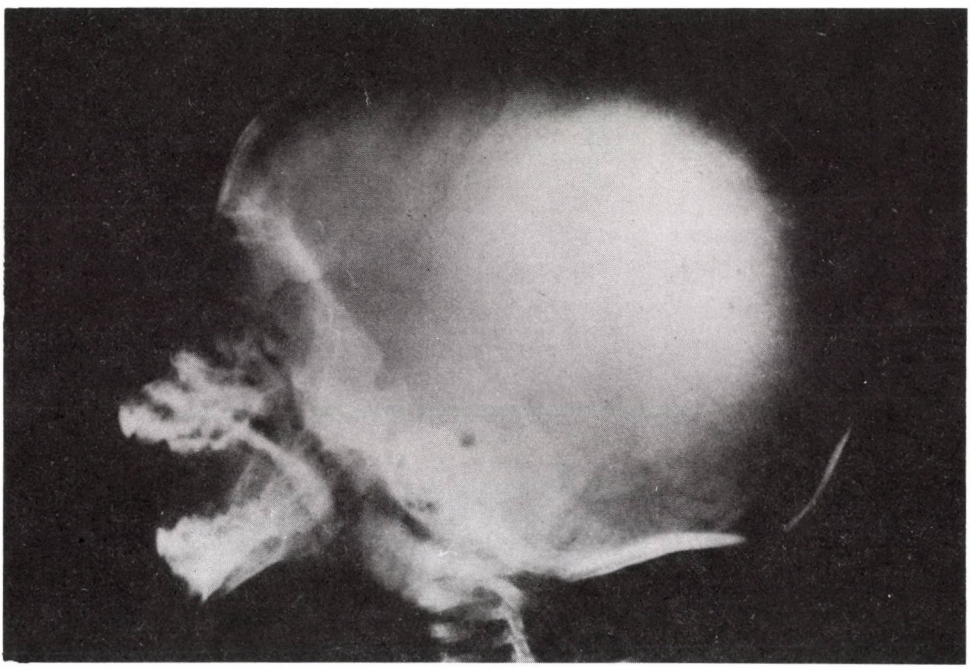

Fig. 3.

Course: due to respiratory and swallowing difficulties the child remained intubated and received parenteral nutrition for 11 days. He had to be fed by tube for the first weeks of life, thereafter bottle feeding was difficult and took about 60 minutes for each meal. At three months, generalized tonic-clonic seizures started, which responded to phenobarbital and valproic acid. His EEG was normal.

During the following three months the child remained stiff, but his motor activities improved gradually. The hips were externally rotated and the extensor posture of the feet disappeared. The baby was able to suck and swallow, but did not develop any mimicry. In prone position he could barely rotate or raise the head and his eyes did not follow objects or faces; the bulbi showed rotatory movements and sometimes diverging/converging strabism but no opsoclonus. He developed an asymmetric (convex to the left) scoliosis of the thorax with a corresponding rib bump and kyphosis of the thoracolumbar

area. Growth retardation, failure to thrive, and microcephalus became more striking.

Before further studies could be performed the patient died in another hospital at the age of nine months. Autopsy revealed severe bronchopneumonia as cause of death. The above described deformities of the spine were confirmed. The brain showed no macroscopic or microscopic abnormalities. The brain weight was normal, muscle tissue was not studied.

DISCUSSION

The British orthopaedic surgeon E.A. Freeman and the paediatrician J.H. Sheldon described the cranio-carpo-tarsal syndrome in 1938 /11/. In 1963 Burian introduced the term "whistling face" /3/.

More than 60 case reports have been published so far. The descriptions show great variability of expression. Wettstein et al /31/ described seven patients within three generations of one family: one of the adults had but the facial characteristics of the WFS. Others describe severely affected newborns with problems of sucking and swallowing and lack of mimicry. These babies later developed deformities of the extremities and spine and sometimes (especially during general anaesthetics) life-threatening bronchopulmonary complications /11,17,19,23,31, our patient/. A "lethal factor" for male patients has been discussed by Wettstein and Antley /2,31/.

Table I classifies the major and minor diagnostic signs of the WFS based on 60 well-documented cases of the literature and our case. The minimal diagnostic criteria for the WFS include the typical appearance of the face plus at least one of the major diagnostic abnormalities of the extremities or the spine. The spine deformities, ptosis of the eyelids, flabby cheeks and H-like dimple of the chin, and particularly the respiratory and feeding difficulties are probably sequelae of a myopathy.

The report of Burian /4/ is the first to emphasize features of a myopathy: flabby musculature of the abdominal wall and the cheeks, which "bulge like a membrane on blowing", a myopathic electromyogram and in muscle biopsy atrophic and vacuolated fibres. Sauk /25/ described a myopathic EMG and connective

TABLE I

Reported major and minor diagnostic signs of the WFS out of 60 well-documented cases in the literuture plus our patient.

Whistling Face Syndrome

Major diagnostic signs	Minor diagnostic signs
Face	
lack of mimicry	feeding difficulties (12/23)
microstoma	high arched palate
"whistling face" (61/61)	long philtrum
	hypoplastic alae nasi
	full flabby cheeks
	H-like dimple of the chin
	supraorbital ridge
	eyelid ptosis
	steep floor of ant. fossa (11/232)
Upper extremity	
ulnar deviation of the fingers (42/46)	contractures of the shoulder
flexion contractures of the fingers (36/41)	impaired rotation of the forearm
	dorsal swelling of the hand
	hypoplasia of the thenar
	flexion contracture of the thumb
Lower extremity	
club foot (24/41)	contracture of the hip and/or
contracture of the toes	contracture of the knee (11/15)
	hypoplasia of m. gastrocnemius
General	
(kypho-) scoliosis (26/31)	growth failure (16/26)
	thin oar-like ribs
	microcephalus (7/16)
	mental retardation (8/26)
	seizures (3/16)

tissue substitution in the muscles of his patient in 1974 and discussed a primary myopathy and/or muscle hypoplasia as the cause of his patients hand- and foot- deformities.

The percentage of lethal pneumonia and unexplained deaths in infancy may have been caused by involvement of the intercostal muscles, as mentioned first by Frazer /10/.

MacLeod noticed "fixed ribs in horizontal position throughout the respiratory cycle" in his patient /17/, who subsequently developed bronchopneumonia. Five (4 males, 1 female) of 61 patients diagnosed at birth developed pneumonia before the age of nine months /11,19,23,31, our patient/, three of them (all males) died. Our patient also died of a severe bronchopneumonia. After the second year of life bronchopulmonary infections are not mentioned. In the 60 reported cases there were two (1 male, 1 female) stillborn and three (males) died before the fifth week of life from unknown causes /9,14,27/.

Respiratory failure after birth, which may even lead to tracheostomy, and recurrent severe respiratory tract infections in infancy are typical for some congenital myopathies /8/.

This point is emphasized by some deaths in infancy (3 of 60 patients referenced in the bibliography and our patient) and improvement after the second year of life. Recently Vanek considered the possibility of a primary myopathy in 1986 because he found centrally placed nuclei and moth-eaten necrosis, hypotrophy of type-I- and hypertrophy of type-II-muscle-fibres, and swollen mitochondriae in the biopsy material of two patients. He interpreted these findings as congenital fibre dysproportion /8,27/.

The long philtrum is probably caused by the characteristic shape of the mouth. Other symptoms, however, such as the supraorbital crease, the steep fossa cerebri anterior /11/, the high arched palate, the hypoplasia of the alae nasi, the small oar-blade-like ribs, and particularly the mental retardation, the seizures, and the microcephaly cannot be explained on this basis and imply a more complex pathogenesis of this syndrome.

The reports of mostly autosomal dominant as well as recessive inheritance /1,9,14,25/ and of sporadic cases suggest a genetic heterogeneity. In 1982 Hall /13/ figured out 23 autosomal dominant and 18 sporadic cases in the total number of 41 reported patients. The stigmata of the mother and the maternal grandfather of our patient support the autosomal dominant inheritance of the WFS. Chromosome analysis were normal in most cases /5,6,10,14,22,24,25,30/, but one XO configuration (Turner syndrome) /3/ and one abnormally long paracentric secondary constriction in one of the C-group chromosomes is described /23/.

Despite microcephaly, mental retardation and lack of movement, the presence of contractures, ulnar deviation, whistling face, and normal tendon reflexes at birth exclude a hypoxic cause in this condition.

The following disorders should be excluded when the diagnosis of WFS is considered:

- Distal arthrogryposis (DA): In 1982 Hall /13/ designated the DA type I and type II (A-E, with additional findings). She found out at least 4 of the reported WFS patients to be cases of DA. Thus, because of an overlap of manifestations with the WFS the DA (particularly type I and II B) has to be ruled out carefully.
- Congenital dystrophia myotonica: This condition with generalized muscle hypotony has no characteristic facial abnormalities. Since the biopsy findings may somehow resemble a WFS, it should be excluded by EMG.
- The mitochondrial myopathies should remain in consideration because of the reported mitochondrial abnormalities in the WFS /27/.

Treatment for the WFS remains symptomatic. It seems important to deal adequately with the early respiratory complications. There are no primary skeletal changes of the extremities but marked posture abnormalities at birth. Thus, the secondary changes may develop due to the "skelet forming power of the muscles" (Moss's theory, cited by Vanek /27/. Patients develop joint contractures which may be resistent to

therapy, as seen particularly in myopathies /8/. If physiotherapy cannot prevent a contracture, it has to be corrected surgically.

In our case we missed the opportunity for a muscle biopsy. However, it should be performed in all suspected cases, and biochemical and histochemical studies should be done to further define the aetiology of WFS.

REFERENCES

1. Alves AFP, Azevedo ES: Recessive form of Freeman-Sheldon's syndrome or "whistling face". J Med Genet 14: 139, 1977

2. Antley RM, Uga N, Burzynski NJ, Baum RS, Bixler D: Diagnostic criteria for the whistling face syndrome. Birth Defects: Original Article Series 11: 161, 1975

3. Bajaj M, Mehta L: Freeman-Sheldon (Whistling face) syndrome in a Turner mosaic. J Med Genet 21: 398, 1984

4. Burian F: The "whistling face" characteristic in a compound cranio-facio-corporal syndrome. Brit J Plast Surg 16: 140, 1963

5. Cervenka J, Gorlin R, Figalova P, Farkasova J: Craniocarpotarsal dysplasia of whistling face syndrome. Arch Otolaryngol 91: 183, 1970

6. Cirillo-Silengo M, Davi GF, Bianco R, DeMarco A, Costa M, Franceschini P, Bonenti G: Sindrome di Freeman-Sheldon con ritardo mentale. Min Ped 34: 277, 1982

7. Cox DW, Pearce WG: Variable expressivity in craniocarpotarsal dysplasia. Birth Defects: Original Article Series 10: 243, 1974

8. Dubowitz V: The congenital myopathies. In: Muscles disorders in childhood. WB Saunders Company Ltd. London Philadelphia Toronto, pp 93-104, 1978

9. Fitzsimmons JS, Zaldua V, Chrispin AR: Genetic heterogeneity in the Freeman-Sheldon syndrome: Two adults with probable autosomal recessive inheritance. J Med Genet 21: 364, 1984

10. Fraser FC, Pashayan H, Kadish M: Cranio-carpo-tarsal dysplasia. Report of a case in father and son. J Am Med Ass 211: 1374, 1970

11. Freeman EA, Sheldon JH: Cranio-carpo-tarsal dystrophy. An undescribed congenital malformation. Arch Dis Child 13: 277, 1938

12. Gross-Kieselstein E, Abranhamov A, Ben-Hur N: Familial occurrence of the Freeman-Sheldon syndrome. Pediatrics 47: 1064, 1971

13. Hall JG, Reed SD, Greene G: The distal arthro gryposes: Delineation of new entities - Review and nosologic discussion. Am J Med Genet 11: 185, 1982

14. Kousseff BG, Connachie P, Hadro TA: Autosomal recessive type of whistling face syndrome in twins. Pediatrics 69: 328, 1982

15. Kratzer W, Borm U: Cranio-carpo-tarsales Dysplasia Syndrome (Whistling face - Syndrom nach Freeman und Sheldon). Monatschr Kinderheilkd 126: 277, 1978

16. Külz J: Das Freeman-Sheldon Syndrom. Medizin im Bild 4: 78, 1961

17. McLead P, Patriquin H: Whistling face syndrome - cranio - carpo - tarsal dysplasia. Clin Ped 13: 184, 1974

18. O'Connell DJ, Hall CM: Cranio - carpo - tarsal dysplasia. Ped Radiol 123: 719, 1977

19. Otto FMG: Die "Cranio-carpo-tarsal dystrophie" (Freeman und Sheldon). Ein kasuistischer Beitrag. Zeitschr Kinderheilkd 73: 240, 1953

20. Pfeiffer R, Ammermann M: Das Syndrom von Freeman und Sheldon - drei neue Beobachtungen. Zeitschr Kinderheilkd 112: 43, 1972

21. Pitanguy I, Bisaggio S: A chiro-cheilo-podalic syndrome. Brit J Pals Surg 22: 79, 1969

22. Predescu V, Christodorescu D, Sirbu C, Ionescu R: Craniofacial dysmorphism with digital abnormalities, oligophrenia and neurological disturbances - a variant of the Freeman-Sheldon syndrome? Revue Roumanie de Medicine Neurologie et Psychiatrie 13: 127, 1975

23. Rintala AE: Freeman-Sheldon's syndrome. Cranio - carpo - tarsal dystrophy. Acta Paed Scand 57: 553, 1968

24. Sanchez JM, Kaminker CP: New evidence for genetic heterogeneity of the Freeman-Sheldon syndrome. Am J Med Genet 25: 507, 1986

25. Sauk I, Delaney JR, Reaume CH, Brandjord R, Witkop CJ: Electromyography of oral-facial musculature in craniocarpotarsal dysplasia (Freeman-Sheldon syndrome). Clin Genet 6: 132, 1974

26. Shamra RN, Tandon SN: "Whistling face" deformity in compound craniofacio-corporal syndrome. Brit Med J 4: 33, 1970

27. Vanek I, Jand AJ, Ambrelova V, Losan F: Freeman-Sheldon syndrome: a disorder of congenital myopathic origin? J Med Genet 23: 231, 1986

28. Walbaum R, Lejeune M, Poupard B, Lacheretz M, Fontaine G: Le syndrome de Freeman-Sheldon (syndrome du siffleur). Ann Péd

29. Walker BA: I. Whistling face - windmill vane hand syndrome (craniocarpotarsal dystrophy: Freeman-Sheldon syndrome). Birth Defects: Original Article Series 5: 228, 1969

30. Weinstein S, Gorlin RJ: Cranio-carpo-tarsal dysplasia or the whistling face syndrome. I. Clinical considerations. Am J Dis Child 117: 427, 1969

31. Wettstein A, Buchinger G, Braun A, Bazan UB: A family with whistling face syndrome. Hum Genet 55: 177, 1980

M.M. MILLNER, MD
A-8036, Graz
Österreich