Hallermann-Streiff Syndrome

Clinical and Prognostic Considerations

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A patient with the Hallermann-Streiff syndrome showed significant findings, including demonstration of decreased thoracic compliance and a marked response of growth hormone to arginine stimulation. No metabolic or chromosomal defect could be demonstrated in this patient.

A combination of clinical findings now most commonly called the Hallermann-Streiff syndrome in the American literature and the dyscephalic syndrome of Francois in the European literature consists of the following: (1) dyscephaly with bird facies and hypoplastic mandible, (2) proportionate nanism, (3) congenital cataracts, (4) microphthalmia, (5) hypotrichosis, (6) dental anomalies, (7) cutaneous atrophy, limited to the face and/or scalp, (8) frontal or occipital bossing, (9) open sutures and fontanelles, (10) high arched palate, and (11) nystagmus. Francois considers the first seven features essential.[1] However, like many such syndromes, reported cases frequently do not demonstrate all manifestations. Moreover, nanism was not mentioned in one of the two original patients described by Hallermann.[2]

Report of a Case

This male infant weighed 2.3 kg (5 lb 1½ oz) at birth and was born to a 22-year-old, gravida 1, para 0, white mother and a 24-year-old white father who deny consanguinity. The length of gestation was 40 weeks. The prenatal course, labor, and delivery were uneventful and the infant's Apgar score at birth was 7, with respiration being established immediately.

Physical examination at birth revealed a low birth weight male infant in no distress. His length was 45.7 cm (18½ inches); his head circumference was 30.5 cm (12 inches); and his chest circumference was 25.4 cm (10½ inches). The crown to symphysis pubis/symphysis pubis to heel (U/L) ratio was 1.79. The length to arm span ratio was 1.04. Of note, were dyscephaly with bird facies, micrognathia, and glossoptosis (Fig 1 to 3). The cranial sutures including the metopic and squamosal were widely separated, and the fontanelles were large. Frontal and occipital bossing and craniotabes were noted. Skin over the scalp was atrophic, and there was hypotrichosis of the scalp, eyelashes, and eyebrows (Fig 1 and 2). There was striking microphthalmia with a corneal diameter of 7 mm, and the eyes also appeared proptotic; sclerae were blue and funduscopy was normal. The nose was thin and beaklike with marked cutaneous atrophy (Fig 1 to 3). There was a small midline cleft of the lower lip and a high arched grooved palate. A natal tooth in the No. 24 position was present. The chest was relatively small, and there was a mild pectus excavatum deformity (Fig 1); respirations appeared shallow, and the respiratory rate was 44 per minute. Auscultation of the lungs and heart was unremarkable. Examination of the hands demonstrated shortening of both thumbs.

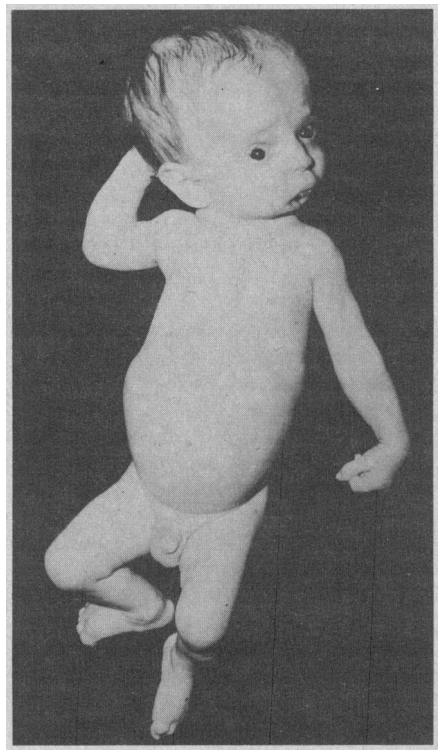
The father was 167.6 cm (5 ft 6 inches) and the mother was 165.1 (5 ft 5 inches). Neither exhibited any of the clinical features noted in the infant and there was no family history of this condition.

Results of laboratory studies at birth, including hemogram, serum electrolytes, calcium, phosphorus, glucose, alkaline phosphatase, urea nitrogen and Venereal Disease Research Laboratory test were within normal limits. Urinalysis was normal and the ferric chloride test on the urine was negative. Urinary mucopolysaccharides, calcium, and phosphorus were within normal limits for age. Quantitative serum and urinary amino acids were likewise within normal limits for age. Chromosomal analysis by peripheral leukocyte culture revealed a normal male chromosome complement (46 XY).

Roentgenograms of the skull showed absence of the angle of the mandible, widely separated sutures, large fontanelles, extremely thin cortex of the skull, and wormian bones in the parietal areas bilaterally (Fig 4). Skeletal survey revealed hypoplastic ribs and clavicles, particularly at the acromial ends (Fig 5). There was shortening of the first metacarpal bilaterally. The cardiothoracic ratio was 0.65, and the cardiac configuration was unusual (Fig 5).

At 8 weeks of age, a routine follow-up skeletal survey revealed a fracture of the left radius. There was no history of even minor trauma. This healed without residua. At 3 months of age, an intumescent

Fig 1.—Patient, age 7 months, Bird facies, micrognathia, high U/L ratio, small chest with pectus excavatum deformity.



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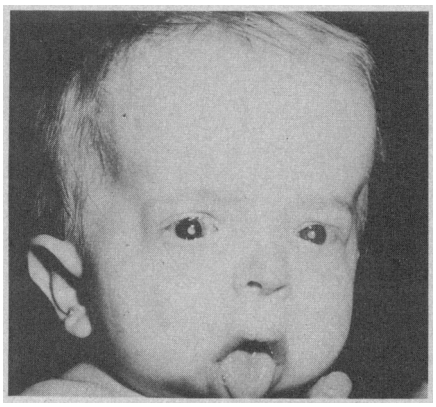


Fig 2.—Front view. Bird facies, hypoplastic mandible, congenital cataracts, microphthalmia, hypotrichosis, frontal and occipital bossing, glossoptosis, cutaneous atrophy over nose.

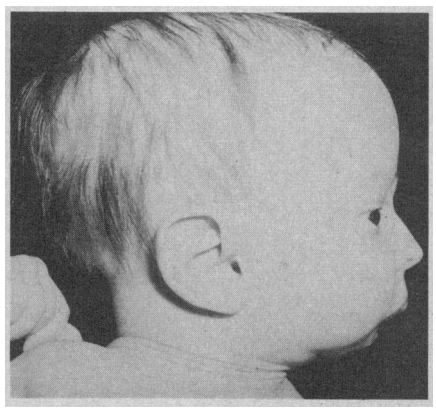


Fig 3.—Side view. Bird facies, hypoplastic mandible, hypotrichosis.

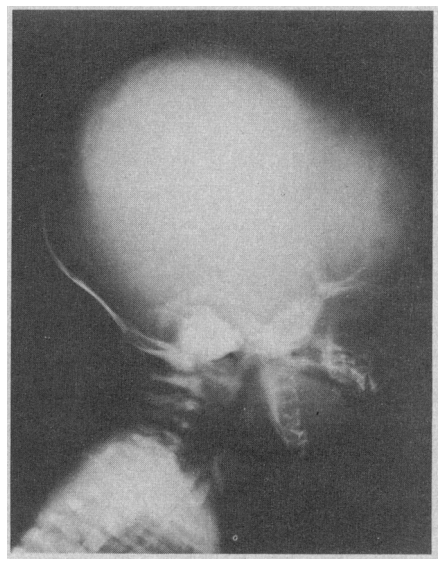
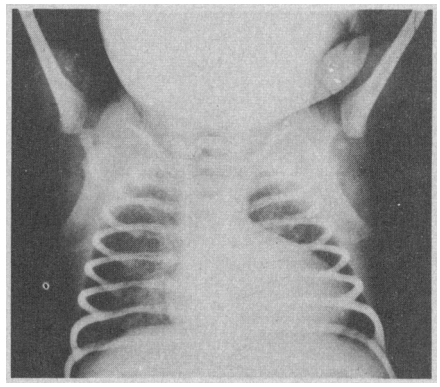


Fig 4.—Lateral roentgenogram of skull at birth. Absence of angle of mandible, widely separated sutures, large fontanels, thin cortex of skull.

Fig 5.—Chest roentgenogram at birth. Hypoplastic ribs and clavicles, cardiothoracic ratio 0.65, with unusual cardiac configuration.



cataract was first noted in the left eye, and at 6 months a similar defect involved the right eye. The right cataract was aspirated at 8 months, and the left was similarly aspirated at 11 months. At 5 months of age the patient developed gradually increasing tachypnea, tachycardia, and hepatosplenomegaly. Auscultation of the heart was still unremarkable. The electrocardiogram indicated biventricular hypertrophy, but neither the size nor configuration of the heart had changed on roentgenogram from birth. The patient was believed to have congestive heart failure, so digitalization was initiated with a very gradual response noted during the following two weeks; however, hepatomegaly persisted for two months.

At 7 months of age, a right sided cardiac catheterization was performed. No anatomic defects were demonstrated, but emptying of the left ventricle appeared to be marginally suboptimal with an estimated ejection fraction of 50% to 60%. Also, decreased compliance of the thorax or intrathoracic structures was suggested by wide respiratory variations on pressure tracings.

At 9 months of age, results of the following studies were normal; hemogram, serum electrolytes, calcium, phosphorus, glucose, alkaline phosphatase, acid phosphatase, blood urea nitrogen, creatinine, total serum protein and albumin-globulin ratio, total serum bilirubin, serum glutamic oxaloacetic transaminase, lactic acid dehydrogenase, creatinine phosphokinase, protein-bound iodine, and butanol-extractable iodine. The urinalysis was normal, and a result of the urine ferric chloride test was again negative. Urinary 17-hydroxycorticosteroids, 17-ketosteroids, and mucopolysaccharides were within normal limits for age. Quantitative serum and urinary amino acid studies were again obtained, and results were within normal limits for age. Growth hormone assay with arginine stimulation increased from 5 ng units to 33 at two hours after infusion.

At 13 months of age the height was 58.4 cm (23½ inches), and the weight was 4.9 kg (10 lb 13 oz). Bone age at this time was 6 to 9 months.

Comment

Our survey of the American and European literature yielded 50 probable cases of Hallermann-Streiff syndrome. The reported clinical findings are summarized in Table 1.[1-29] There has been no similar review since the 21 cases collected by Francois in 1958.[19]

The present case demonstrates almost all of the clinical and roentgenographic manifestations of this syndrome. Numerous laboratory studies failed to reveal the presence of any metabolic abnormality; however, two findings are of interest. Plasma growth hormone was markedly elevated following arginine infusion. This observation demonstrates that the patient did not have a deficiency of growth hormone to account for his short stature. Data from cardiac catheterization suggested decreased thoracic compliance. This may have been a contributory factor in the development of pulmonary infection causing the early death reported in cases 49 and 50 and necessitating tracheostomy in cases 30 and 34.

The difficulty in evaluating this syndrome from reported cases is that there is no specific clinical or laboratory test to categorize definitely these patients together. Most reports of Hallermann-Streiff syndrome are found in the ophthalmology literature and are concerned primarily with the eye abnormalities. Since a

Table 1.—Major Clinical Findings Associated With Hallermann-Streiff Syndrome[1-29]

	Age (yr)	Sex	Bird Facies	Hypoplastic Mandible	Proportionate Nanism	Congenital Cataracts	Microph-thalmia	Hypotrich-osis	Dental Anomalies	Cutaneous Atrophy
1. Aubry, 1893	16	M	+	+	?	+	?	+	+	+
2. Bergmeister, 1911	12	F	+	+	+	+	+	+	+	?
3. Schondel, 1943	12	F	+	+	+	−	+	+	+	+
4. Schondel, 1943 and Gregersen, 1956	8	M	+	+	+	+	+	+	+	+
5. Moehlig, 1946	5	M	+	+	+	+	?	+	+	+
6. Hallermann, 1948	25	M	+	+	+	+	+	+	+	+
7. Hallermann, 1948	55	M	+	+	?	+	+	+	+	+
8. Marchesani, 1949	?	M	−	+	?	+	+	+	+	?
9. Marchesani, 1949	?	M	+	+	?	+	+	?	+	?
10. Streiff, 1950	31	F	+	+	+	+	+	+	+	+
11. Korting, 1950	15	M	+	+	?	+	+	+	+	+
12. Pau, 1950	26	M	+	+	?	+	+	?	?	?
13. Pau, 1950	46	F	+	+	?	+	−	?	?	?
14. Ullrich, 1953	27 mo	F	+	+	?	+	+	+	?	+
15. Weyers, 1954	16	M	+	+	−	+	+	+	+	+
16. Nizetic, 1954	11	M	+	+	+	+	?	−	+	+
17. Becker, 1954	NB	M	+	+	+	+	?	−	?	?
18. Gregory, 1955	7	F	+	+	+	+	?	+	+	+
19. Gregory, 1955	10	F	?	+	+	+	?	+	?	?
20. Leffertstra, 1956	31	M	+	+	+	+	+	+	?	?
21. Gregersen, 1956	25	F	+	+	+	+	+	+	?	+
22. Blodi, 1957	37	F	+	+	+	+	+	+	?	?
23. Blodi, 1957	8	F	+	+	+	+	+	+	+	+
24. Francois, 1958	13	M	+	+	+	+	+	+	+	+
25. Ponte, 1958	18 mo	M	+	+	−	+	−	−	+	−
26. Ponte, 1958	15	M	+	+	−	+	−	−	+	−
27. Ponte, 1958	17	M	+	+	−	+	−	−	+	−
28. Balen, 1959	14	F	+	+	−	+	+	−	−	−
29. Balen, 1959	7	M	+	+	−	+	+	+	+	+
30. Balen, 1959	21 mo	M	+	+	?	+	+	+	+	+
31. Balen, 1959	3 mo	M	+	+	?	+	?	?	+	?
32. Falls, 1960	30	F	+	?	+	+	+	+	+	+
33. Falls, 1960	5 mo	M	+	+	?	+	+	+	+	+
34. Falls, 1960	5 wk	M	+	+	+	+	+	?	+	?
35. Falls, 1960	5 mo	F	+	+	+	+	+	?	?	+
36. Falls, 1960	6	M	+	+	+	+	+	+	+	+
37. Bonamour, 1960	5	F	+	+	+	+	+	+	+	+
38. Calmettes, 1960	16	M	+	+	−	+	+	+	+	+
39. Francois, 1961	?	?	+	+	+	+	+	+	+	+
40. Carones, 1961	8	M	+	+	+	+	+	+	+	+
41. Larmande, 1961	?	?	+	+	+	+	+	+	+	+
42. Larmande, 1961	?	?	+	+	+	+	+	+	+	+
43. Ponte, 1962	33	F	+	+	+	+	+	+	+	+
44. Guyard, 1962	9	F	+	+	+	+	+	+	+	+
45. Guyard, 1962	44	M	+	+	+	+	+	+	+	+
46. Manzitti, 1963	5	M	+	+	+	+	+	+	+	+
47. Manzitti, 1963	7	M	+	+	+	+	+	+	+	+
48. Hoefnagel, 1965	1	F	+	+	+	+	+	+	+	?
49. Hoefnagel, 1965	5 mo	M	+	+	+	+	+	+	+	?
50. Hoefnagel, 1965	3 mo	F	+	+	?	+	+	+	+	?

constellation of anomalies is present and numerous organ systems are involved usually from the outset, patients with this syndrome may frequently be seen first by the pediatrician. He should be most aware of all of its clinical manifestations so that he may establish a definitive diagnosis, anticipate complications, and render prognosis and genetic counseling.

The mechanism of inheritance in the Hallermann-Streiff syndrome is not clear. Most reported cases thus far are sporadic with family histories

Table 2.—Reported Visual Acuity Following Removal of Cataracts in Patients With Hallermann-Streiff Syndrome

Case*	Visual Acuity: Left Eye	Visual Acuity: Right Eye
4 Schondel[5]	20/400	20/400
6 Hallermann[2]	20/140	0
7 Hallermann[2]	4/400	20/400
10 Streiff[9]	0	0
16 Nizetic[14]	20/200	20/40
18 Gregory[16]	20/120	—
19 Gregory[16]	20/200	4/400
20 Leffertstra[17]	1/400	20/40
21 Gregersen[6]	16/400	20/360
22 Blodi[18]	0	0
24 Francois[19]	20/400	10/400
28 Balen[21]	20/20	20/30
29 Balen[21]	7/400	20/200
38 Calmettes et al[24]	20/400	20/400
40 Carones[25]	20/200	20/60
43 Ponte[26]	20/40	2/400
44 Guyard et al[27]	20/50	0
45 Guyard et al[27]	0	0

*Numbers at left correspond to numbers in Table 1.

showing no similarly affected individuals. Only the case reported by Guyard et al[27] and the case followed up by Larmande and described by Francois[1] demonstrated a familial incidence. Two sets of male monozygotic twins have been reported. In one set[5] only one of the twins was affected, while in the other set[21] both infants were involved. There is no apparent sex predilection.

Only two of these individuals have reproduced. One woman (case 43) gave birth to two normal children, and an affected man (case 45) who was "distantly related" to his wife fathered a daughter with positive features (case 44). These are, of course, too few to establish an inheritance pattern. Most of the other individuals were not married so reproductive capacities are unknown.

Life expectancy cannot be determined from the literature, but death from pulmonary infection was reported at age 8 in case 49 and at age 3 in case 50. Case 31 was the monozygotic twin of case 30 and died at age 3 months. The cause of death is not recorded.

Most of the literature on this syndrome is concerned primarily with ocular defects. Eye anomalies include congenital cataracts, microophthalmia, nystagmus, strabismus, chorioretinal atrophy, and peripapillary choroid atrophy. Even with surgical removal of the cataracts, functional results are disappointing. Visual acuity measurements from the literature are summarized in Table 2.

In reports which describe nanism, the height and weight of children usually fall well below 2 standard deviations. Although few adult measurements are available, the average height of girls appears to be approximately 152.4 cm (5 ft) with boys 2.5 to 5.1 cm taller.

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