Medical History

The Proteus syndrome: the Elephant Man diagnosed

J A R TIBBLES, M M COHEN Jr

Abstract

Sir Frederick Treves first showed Joseph Merrick, the famous Elephant Man, to the Pathological Society of London in 1884. A diagnosis of neurofibromatosis was suggested in 1909 and was widely accepted. There is no evidence, however, of café au lait spots or histological proof of neurofibromas. It is also clear that Joseph Merrick's manifestations were much more bizarre than those commonly seen in neurofibromatosis. Evidence indicates that Merrick suffered from the Proteus syndrome and had the following features compatible with this diagnosis: macrocephaly; hyperostosis of the skull; hypertrophy of long bones; and thickened skin and subcutaneous tissues, particularly of the hands and feet, including plantar hyperplasia, lipomas, and other unspecified subcutaneous masses.

Introduction

In the *British Medical Journal* of 6 December 1884 Sir Frederick Treves first reported on "a man who showed an extraordinary appearance owing to a series of deformities."[1] The subject of these deformities was later described in detail in *Transactions of the Pathological Society of London* in 1885 as "a man who earned a living by exhibiting himself as the Elephant Man."[2] At that time no definite diagnosis was reached. In 1909 Parkes Weber first suggested neurofibromatosis as the cause of the Elephant Man's disorder,[3] and this was subsequently widely accepted.

We indicate here the lack of evidence for neurofibromatosis in this patient, compare his condition with that of a patient with the Proteus syndrome, and explain the reasons why we believe that the Elephant Man meets the criteria for the Proteus syndrome.

Case reports

CASE 1

Joseph Carey Merrick was born in 1862 in Leicester, the obstetric history apparently having been normal. At birth he showed no obvious congenital deformities. The family history was negative for neurofibromatosis: both parents and two subsequent siblings showed no evidence of the disease. Deformities developed during early childhood, being noted initially at about 18 months of age, and progressed throughout his life. When he was 20 a large portion of his facial deformity was successfully removed. When he was 22 his case was fully described by Treves,[2] and during the six years of medical follow up his deformities increased in extent until he died, apparently of suffocation, at the age of 28 in 1890.[4]

Examination showed a man of "a little below average height" with a head circumference of 36 inches (91 cm). He was of normal intelligence. Over much of his body the skin was papillomatous and verrucous, and in some areas it was loose and flabby; subcutaneous thickening was evident. The skull was covered with exostoses, and there was localised hypertrophy that was most pronounced in the skull and right arm and over the feet. The skin overgrowths were called dermatolysis and pachydermatoceles.[4] He was examined by the dermatologist H R Crocker in 1885,[5] and neither he nor any other physician ever described café au lait spots. Postmortem casts of the limbs showed "moccasin" feet, a form of plantar hyperplasia (fig 1).

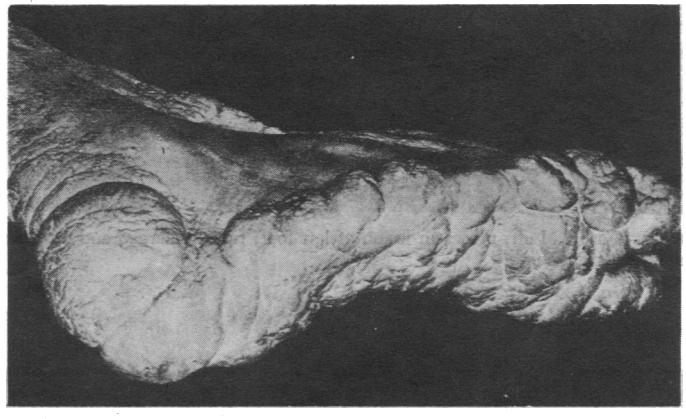

FIG 1—Plaster cast of Joseph Merrick's foot showing moccasin foot, a form of plantar hyperplasia. (From Howell and Ford.[4])

There is no record of a necropsy having been performed, and it is likely that consent was refused. There was never any histological evidence of the presence of neurofibromas. Skin samples from the patient were preserved but lost during the second world war.[4]

CASE 2

We diagnosed the Proteus syndrome in this boy. He weighed 2900 g at birth and was the product of a normal pregnancy and delivery. The neonatal period was complicated by poor feeding, hypoglycaemia, and possible seizures. He was referred as a neonate for investigation of a mildly dysmorphic appearance and vascular naevi of the left leg. The family history was negative for the Proteus syndrome; there was one normal 21 year old sibling, both parents were normal, and there was no consanguinity. The father was 45 and the mother 42 at the time of conception.

On examination at 1 month of age length was 57 cm (75th percentile), weight 3850 g (10th percentile), and head circumference 40 cm (98th percentile). Facial asymmetry was present. The left leg was 1 cm longer than the right. Vascular naevi over the left buttock and left leg and varicosities of the left knee and ankle were noted. The left eye was enlarged, with pallor of the optic disc and a cluster of retinal colobomas inferior to the disc. Computed tomography showed increased ventricular size, increased sulciform markings

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on the left, and possible left hemimegalencephaly. An electroencephalogram was normal.

By 5 months of age he was having occasional seizures and there was global developmental retardation. Thickened, wrinkled skin was becoming apparent over the toes and fingers. Computed tomography at 10 months of age showed clear hemimegalencephaly with ventricular dilatation. By the age of 22 months head size had increased to 53·5 cm and soft tissue masses diagnosed by palpation as lipomas were noted on the chest and abdomen. Kyphoscoliosis was becoming apparent.

At 5½ years of age there was profound developmental retardation and gross asymmetry of the whole body. The discrepancy in the length of the legs was more pronounced. Asymmetric chest and abdomen were associated with kyphoscoliosis. Large lipomas were present on the left abdomen and over the right breast. Overgrown, redundant tissue was observed as a moccasin lesion of the left foot (fig 2), producing gross deformity. The right foot had minor discrepancies in the lengths of the toes and medial overlapping of the second toe. The right hand was enlarged and grossly deformed (fig 2). Linear verrucous epidermal naevi were evident on the left neck and left knee and multiple naevus flammeus-like haemangiomas were present on the left leg, left buttock, and left side of the back and abdomen. Important findings in the head and neck region included macrocephaly, severe craniofacial asymmetry (with the left eye larger than the right), redundant skin around the nose, and a pointed chin (fig 3). Bony hyperostoses were also present, one in the midline just above the nasal bridge and one in the region of each ear.

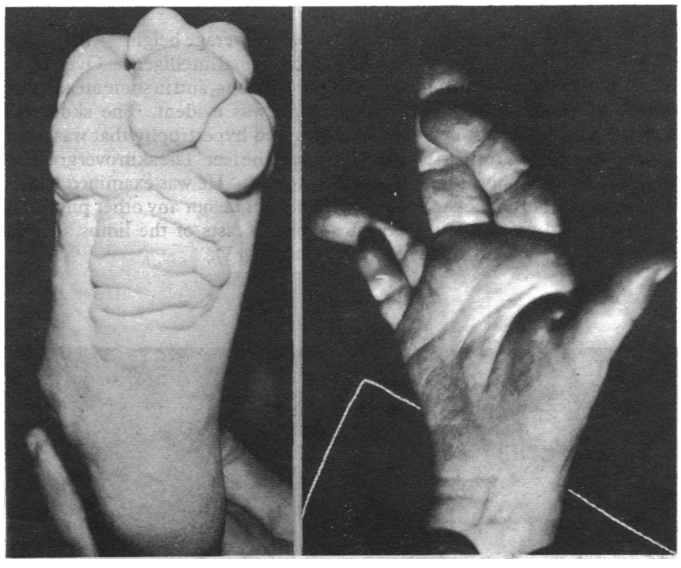

FIG 2—Case 2. Left, moccasin lesion of left foot; right, enlarged and grossly deformed right hand.

Discussion

The term Proteus syndrome was coined by Wiedemann *et al* in 1983 to identify a disorder with protean manifestations including partial gigantism of the hands or feet, or both, asymmetry of the arms and legs, plantar hyperplasia, haemangiomas, lipomas, varicosities, linear verrucous epidermal naevi, macrocephaly, cranial hyperostoses, and "hypertrophy" of long bones.[6] The syndrome was named after the Greek god Proteus (the polymorphous). Although Wiedemann *et al* reported four cases and introduced the term Proteus syndrome, several independent reports (summarised by Costa *et al*[7]) had been published previously. In 1979 one of us reported two cases and recognised that the condition differed from neurofibromatosis, the Klippel-Trénaunay-Weber syndrome, and the Maffucci syndrome.[8] The Proteus syndrome has been reviewed extensively elsewhere.[7,9] The table compares the clinical features in previously reported cases with those in case 1 (Joseph Merrick) and case 2 (our patient). Because the Proteus syndrome is incompletely delineated patients should be carefully monitored for the possible development of other neoplasms as it is obviously a hamartoneoplastic disorder.

All cases to date have been sporadic. Most known hamartoneoplastic disorders are autosomal dominant conditions, and in the case of the Proteus syndrome the patients reported may represent new mutations for a dominant disorder with low reproductive fitness. Neurofibromatosis has been estimated to have the highest mutation rate in man.[10] As several patients with the Proteus syndrome were earlier thought to have had neurofibromatosis it is interesting to speculate that the high mutation rate might conceivably reflect the pooling of several distinct entities, some of which have low reproductive fitness.[8]

In the case of Joseph Merrick there is no evidence of a family history of neurofibromatosis or of café au lait spots in adulthood,

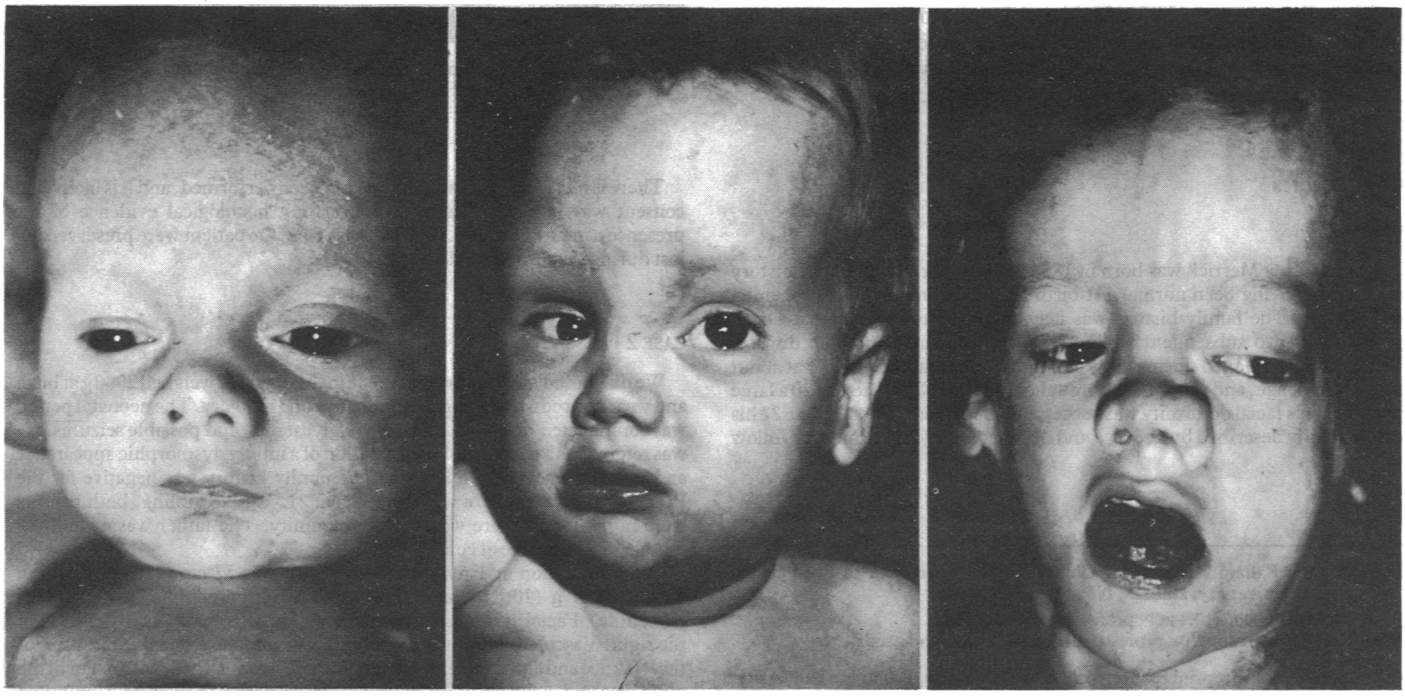

FIG 3—Case 2. Change in facial dysmorphism. Left, age 1 month; centre, age 5 months; right, age 5½ years.

which surely would have been recognised and described by clinicians of the stature of those who examined him, such as the dermatologist H R Crocker (café au lait spots are present in over 99% of patients with neurofibromatosis[11]). Furthermore, there is no histological evidence of neurofibromas. It is also clear that Joseph Merrick's manifestations were much more bizarre than those commonly associated with neurofibromatosis. Merrick had many features of the Proteus syndrome—namely, macrocephaly; thickened skin and subcutaneous tissues, particularly of the hands and feet, including plantar hyperplasia (fig 4), lipomas, and unspecified subcutaneous masses; hypertrophy of long bones; and overgrowth of the skull. Merrick's normal mentation is also compatible with the Proteus syndrome (table).

We therefore contend that there is no positive evidence that the Elephant Man suffered from neurofibromatosis; rather, there is good evidence that he did not and in fact had features that are fully compatible with the Proteus syndrome.

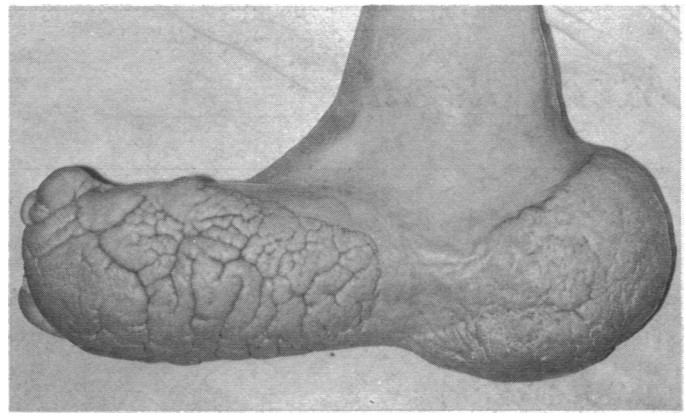

FIG 4—Plantar hyperplasia in a previously reported case. (From Cohen and Hayden.[8])

Clinical features of the Proteus syndrome

	Proportion of previously reported cases with feature	Presence of feature in: Case 1 (Joseph Merrick)	Case 2 (our patient)
Growth:			
Asymmetry of limbs	13/13	+	+
Partial gigantism of hands or feet, or both	12/13	+	+
Skeletal:			
Hypertrophy of bone	13/13	+	+
Hyperostoses of skull	9/13	+	+
Skin:			
Verrucous epidermal naevi	10/12	+*	+
Thickening of skin and subcutaneous tissue	12/12	+	+
Lipomas†	5/11	+	+
Vascular anomalies‡	8/13	+	+
Unspecified subcutaneous masses	10/13	+	+
Craniofacial:			
Macrocephaly	4/7	+	+
Epibulbar tumour	3/13	–	–
Enlarged eye	2/13	–	+
Prognathism	3/11	–	+
Performance:			
Mental deficiency	6/13	–	+
Seizures	2/13	–	+

*Treves spoke of "papillomatous" skin that in one area merged into "a mere roughening of the skin"; this roughening of the skin may have been a verrucous epidermal naevus.
†Pelvic lipomatosis has been found in three cases, thus increasing the total number of patients affected with lipomas.
‡Vascular anomalies include haemangiomas, lymphangiomas, "venous dilatation," "purplish discoloration," and varicosities.

References

1 Anonymous. Reports of societies. Pathological Society of London. *Br Med J* 1884;ii:1135-43.
2 Treves F. A case of congenital deformity. *Transactions of the Pathological Society of London.* 1885;**36**:494-8.
3 Parkes Weber F. Cutaneous pigmentation as an incomplete form of Recklinghausen's disease, with remarks on the classification of incomplete forms of Recklinghausen's disease. *Br J Dermatol* 1909;**21**:49-51.
4 Howell M, Ford P. *The true history of the Elephant Man.* London: Allison and Busby, 1980.
5 Crocker HR. *Diseases of the skin: a review of 15,000 cases of skin disorders.* London: Lewis, 1905.
6 Wiedemann HR, Gurgio GR, Aldenhoff P, Kunze J, Kaufmann HJ, Schirg E. The Proteus syndrome. *Eur J Pediatr* 1983;**140**:5-12.
7 Costa T, Fitch N, Azouz EM. Proteus syndrome: report of two cases with pelvic lipomatosis. *Pediatrics* 1985;**76**:984-9.
8 Cohen MM Jr, Hayden PW. A newly recognised hamartomatous syndrome. *Birth Defects* 1979;**15**(5B):291-6.
9 Lezama DB, Buyse ML. The Proteus syndrome: the emergence of an entity. *Journal of Clinical Dysmorphology* 1984;**2**:10-3.
10 Crowe FW, Schull WJ, Need JV. *A clinical, pathological and genetic study of multiple neurofibromatosis.* Springfield, Illinois: Charles C Thomas, 1956.
11 Riccardi VM. Von Recklinghausen neurofibromatosis. *N Engl J Med* 1981;**305**:1617-27.

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Individual textbooks advocate different dietary restrictions to prevent calcium oxalate renal stones recurring. Some books ignore diet altogether and just recommend increased fluid intake. Others forbid all dairy products, most fruits and vegetables, including citrus and lettuce, as well as chocolate, coffee, tea, and nuts. Have any controlled trials proved the efficiency of these restrictions in preventing recurrences? Do the tea loving British have a specially high incidence of renal calculi in view of the high oxalic acid content of tea?

The link between diet and the occurrence of oxalate calculi is not a simple one and this accounts for the range of advice offered. There is poor correlation between urinary oxalate concentrations and the presence of oxalate calculi but they are occasionally associated with a high oxalate consumption usually from leafy vegetable sources such as spinach and rhubarb. There is no evidence to associate tea consumption with renal calculi. Oxalates in foods are poorly absorbed[1] and this probably accounts for the lack of any real association between intake and any metabolic consequences that might be expected on intuitive grounds.—D A T SOUTHGATE, head, nutrition and food division, Food Research Institute, Norwich.

1 Rodricks JV, Pohland AE. Food hazards of natural origin. In: Robert HR, ed. *Food safety.* New York: Wiley Interscience, 1981:185-6.

What procedure should be followed when a dentist requests vaccination against hepatitis B?

In the United Kingdom the hepatitis B vaccine should be offered to high risk health care personnel, including dentists, without prescreening for hepatitis B virus (HBV) markers since this has not been shown to be cost effective.[1,2] In one study only 6·9% were baseline anti-HBs positive and would therefore have been considered already immune.[1] Subjects who are anti-HBs positive are not infectious "carriers" having cleared the HB virus and do not have liver disease. The vaccine is safe to give to those already HBV-marker positive but having baseline anti-HBs does not appear to confer any specific advantage to the overall levels of anti-HBs achieved after the three dose course.[1] It is more important to test for anti-HBs after the three dose course (usually one to three months after) since 5-10% will be shown to be poor (<50 mIU/ml) or non-responders respectively[1,2] and these are not necessarily protected from HBV infection. Since the anti-HBs levels after vaccination fall exponentially, these should be checked after one to two years to detect when they fall below currently accepted limits, namely, 10-50 mIU/ml. Of those original responders who received a fourth dose, anti-HBs levels rose by more than a thousandfold indicating that the protection may be longer than hitherto realised.[1,2] For the poor and non-responders, antibody levels may rise in some after an additional dose especially if this is delayed beyond one year.[1,2] Currently, the vaccine licensed in the United Kingdom (HBVax; MSD) is recommended to be given at times 0, one, and six months but higher levels of anti-HBs may be achieved if the third dose is delayed to 12 months,[2] and also if the doses are given by injection into the deltoid muscle rather than the buttock.[3]— ELIZABETH FAGAN, lecturer, liver unit, London.

1 Fagan EA, Tolley P, Smith HM, *et al.* Hepatitis B vaccine: immunogenicity and follow-up including 2 year booster doses in high-risk healthcare personnel in a London teaching hospital. *J Med Virol* (in press).
2 Jilg W, Schmidt M, Deinhardt F. Immune responses to late booster doses of hepatitis B vaccine. *J Med Virol* 1985;**17**:249-54.
3 Morbidity and Mortality Weekly report (MMWR). Suboptimal response to hepatitis B vaccine given by injection into the buttock. *MMWR* 1985;**34**:105-8.