Bloch-Sulzberger Syndrome (Incontinentia Pigmenti)

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The Bloch-Sulzberger syndrome is a rare disease. It presents at or soon after birth with erythema and blistering of the skin, which leave pigmented scars of characteristic swirling pattern, which gradually fade (Bloch, 1926; Sulzberger, 1927). In addition, a number of other abnormalities occur with varying frequency. These include dental aberrations (Gorlin and Anderson, 1960), eye defects (Scott, Friedmann, Chitters, and Pepler, 1955), mental deficiency (Carney, 1951), and paralyses.

A case is reported of a young girl who presented with this syndrome, showing skin, tooth, and hair defects. The family came to the notice of one of us (N.S.) because of dental troubles in the proband, and to the other (A.E.H.E.) through a maternal aunt who sought genetic counselling advice.

Case Report

Personal History. M.A.C., a female child born February 20, 1959, was first seen in November 1962 when she was referred from an infant welfare clinic because she lacked some teeth. Her previous medical history revealed that she was born at term (birth weight 3571g.), and that she developed blisters on her trunk and neck within 24 hours. The blistering, accompanied by an increasing degree of pigmentation, continued for about 5 weeks. The vesiculation then subsided. During infancy some degree of verrucosity was apparent at the sites of the original lesions. The child was examined on April 24 by a consultant paediatrician, who reported that her general development appeared to be normal. Since then she has continued to grow and develop normally. The child is now a pleasant little girl of apparently average intelligence. She attends her local infants' school and is thought by her mother to be slow but not backward.

She has an elfin facies and there is pigmentation and scarring over the whole of her upper lip and on the right side of her chin (Fig. 1). The skin of her upper lip is thin, atrophic, and faintly reddish-brown with reticular markings. On her trunk there are faint, ill-defined

whorls, lines, streaks, and irregular reticulated areas of thin, very faintly coffee-coloured scars which are found on both flanks extending up to the axillae, down to the rib margins, and medially towards the nipples (Fig. 2).

Inside her mouth the lack of teeth is obvious. The dental formula is as follows:

Teeth erupted	$\begin{array}{c ccc} E & C & A & \\ \hline CBA & & & \end{array}$	$\begin{array}{c ccc} A & CE6 & & \\ \hline ABC & & & \end{array}$
teeth unerupted	$\begin{array}{c ccc} 6 & 3 & 1 & \\ \hline 6 & 321 & & \end{array}$	$\begin{array}{c ccc} 1 & 3 & & \\ \hline 123 & 6 & & \end{array}$

(Letters A-E refer, in turn, to the deciduous teeth, i.e. central and lateral incisors, canines, and first and second molars. Numbers 1-8 refer to the permanent teeth, central and lateral incisors, canines, two premolars, and three molars.) She has never had teeth extracted, and

FIG. 1. Proband. The lesion on the right side of the chin is clearly visible.

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FIG. 2. Swirling pattern of pigmentation on the trunk.

FIG. 3. Intra-oral photograph of upper jaw. (Radiographs of the posterior teeth showed absence of premolars.)

the teeth she has are well shaped and free from caries (Fig. 3). Where the teeth are missing, the alveolar ridges have failed to develop and are like those found in adults long after their teeth have been extracted.

Her hair is a mousey, fair colour. The hair near her face is mostly soft with a slight wave; however, there are a few areas about 3 mm. diameter where it grows in different directions from the surrounding hair. At the back of her head, the hair is entirely irregular in its lie. There is a patchy alopecia which is most marked at the vertex. The largest bald area is about 25 mm. in diameter, the others are much smaller. Her eyebrows are scanty and altogether absent on the lateral aspects. Although her upper eyelashes are normal, there are very few on the lower eyelids.

Apart from requiring glasses for short sight, her eyes are normal. Her pupils are round and identical in size. She has no nystagmus, nor does she have a strabismus. The ocular fundi are normal.

The rest of the clinical examination was normal and in particular there was no evidence of any cardiovascular or neurological abnormality.

Family History (Fig. 4). The proband's mother (III.4) has never had any of the skin lesions that occur in the Bloch-Sulzberger syndrome. She has been almost completely blind in the right eye for as long as she can remember, and at the age of 13 years a lenticular opacity was removed from this eye but it did not improve her vision. On examination, she has a right micro-

phthalmos with internal strabismus, and the ocular fundus appears perfectly normal. In the left eye there is nystagmus in all directions of gaze, the visual acuity and field of vision are normal as is the appearance of the retina. Apart from a slight degree of scoliosis the rest of the clinical findings are normal. Her first two pregnancies (IV.1 and IV.2) terminated in miscarriages at 5 months. The first was a male but the sex of the second was not recorded in the hospital notes, though the mother was led to believe that it was also a male. The condition of neither of these foetuses is known. Besides the proband she has two other children (IV.3) and IV.5) who appear to be normal on clinical examination.

A maternal aunt (III.6) has been troubled with blurred vision in her right eye for the past 15 years, but in all other respects she has been healthy. On clinical examination no explanation could be found for her complaints. She has been married for 5 years but has avoided pregnancy because she fears she may transmit the disease to her children.

Two maternal uncles (III.7) and (III.8) show deutan colour defects and the left leg of the third (III.9) is slightly shorter than the right, attributed to a polio infection in childhood.

The maternal grandmother (II.5) has arthritis but is healthy otherwise. II.1 committed suicide, II.6 was killed during the war, and II.7 and II.8 both died from tuberculosis.

Discussion

In 1906 Garrod reported a 2½-year-old girl who had skin lesions very similar to those later described by Bardach in 1925, which she referred to as 'systematic naevus formation', and which seems to be the same condition that Bloch (1926) demonstrated before the Swiss Dermatological Society in Basle. Bloch's case suffered from a pigmentation disorder which he thought had not previously been

FIG. 4

described. He called the disease 'Incontinentia Pigmenti', because of the histological picture. However, Haber (1952) pointed out that lichen planus, lupus erythematosus, Civatte's poikiloderma, Jacobi's poikiloderma, and Riehl's melanosis all show pigmentation based on a similar mechanism, and the name Bloch-Sulzberger syndrome is therefore preferable. Bloch's case was later fully described and discussed by Sulzberger (1927).

The diagnosis of the disease usually depends on the presence of the easily recognized skin lesions. These are associated with a variety of other defects that are almost entirely restricted to the skin, its appendages, the eyes, and the central nervous system. Congenital heart disease and chondrodysplasia have been reported, but the incidence is low.

Skin Lesions. It is possible to divide the skin lesions in Bloch-Sulzberger syndrome into four stages (Butterworth and Streat, 1962):—an inflammatory stage characterized by erythema, vesicles, and bullae; a hypertrophic stage with the formation of papules; a stage of pigmentation when the typical swirling pattern of pigmentation is found; and finally the stage of involution when the affected areas of skin become depigmented. The colour of the lesions is brown, slate grey, or a dull yellowish tint. The pigmentation forms a bizarre pattern of lines, streaks, and whorls, which appear to be randomly arranged, though they may be of a somewhat symmetrical distribution (Bloch, 1926). The

skin lesions in the case described here are typical of the Bloch-Sulzberger syndrome. The patterns show a great similarity to those in the illustrations to Bardach's and Sulzberger's papers.

Dental Anomalies. Odontopenia* is not infrequent. Franklin (1952), when reviewing 29 reports of the Bloch-Sulzberger syndrome, mentioned that 'dental hypoplasia' was among the associated congenital defects. Gorlin and Anderson (1960) found reports of deviations from the accepted normal dentition in 25 out of a 100 cases reported up to that time. Their analysis of these was restricted by lack of radiographs, photographs, or adequate descriptions of the dental condition in many. They listed the abnormalities as:—(1) delayed eruption of teeth, (2) 'pegged teeth', (3) missing teeth, (4) 'malformed' teeth, (5) family history of 'hypodontia'. At the same time they reported two further cases with dental abnormalities and gave a description of the dental condition of a third. Hitchin and Halperin (1964) reported another case with 'partial anodontia' and discussed the other diseases in which this occurred.

Hair. The condition of the child's hair has been reported on by Dr. P. B. Mumford who agreed

* Several terms have been used to describe the condition in which there is a failure of development of the teeth. Odontopenia seems to be neater and more appropriate than the others.

that the lie of the hair was strange but could find no abnormality of its structure. There appears to be no other published report of irregular lie of the hair in the Bloch-Sulzberger syndrome. The areas of alopecia in our case are probably the result of secondary infections of the early lesions of the scalp. There is no sign of the pseudo-pelade type of alopecia described in other reports of the Bloch-Sulzberger syndrome. Bardach (1925) reported the retention of lanugo hair in the twins she described. She did not, however, see them after 6 weeks of age, when they were transferred to the care of another department. Various skeletal and neurological abnormalities have occasionally been described in patients with the Bloch-Sulzberger syndrome as well as mental retardation and epilepsy (Jackson and Nigam, 1962).

Ocular Lesions. Eye defects are found quite frequently in association with the syndrome. Bloch and Sulzberger's case was referred to them by an ophthalmologist to whom the child was sent for treatment of retrobulbar glioma (Bloch, 1926) or retinal detachment (Sulzberger, 1927). Bardach's twins are described as having star-shaped irises. More recently Findlay (1952) found eye defects described in 8 of 25 reported cases, and Scott *et al.* in 1955 found eye defects in 24 out of 92 reported cases, and these included nystagmus, strabismus, cataract, optic nerve atrophy, glioma and pseudo-glioma, and retinal detachment.

Genetic Aspects. There are numerous reports of several members of a family being affected with the Bloch-Sulzberger syndrome (Bardach, 1925; Franklin, 1952; Calnan, 1952; Rozehnal and Vodička, 1957; Marty, Bechtel, and Wood, 1958; Jackson and Nigam, 1962; Küster and Olbing, 1964); and Jackson and Nigam (1962) have reviewed many of the earlier reports of familial cases. The disease is clearly familial, but the mode of inheritance is uncertain, and there are several possibilities.

(i) It has been suggested that the syndrome is inherited as an X-linked dominant trait with lethality in the hemizygous male (Lenz, 1963). In favour of this idea are the observations that the disease very rarely affects males, and is transmitted by affected females who have a deficiency of males among their offspring, and an unusually high frequency of abortions that are possibly hemizygous males. So far, about 100 cases have been reported of which no more than 5 have been males (Oldfelt, 1959). The characteristic pattern of pigmentation

in affected females might be explained in terms of the Lyon hypothesis concerning gene action in the X chromosome (Lyon, 1962). Possibly the pigmented areas represent those cells in which the active X chromosome is the one bearing the gene for the Bloch-Sulzberger syndrome (McKusick, 1962). Random inactivation of the X chromosome may be a possible explanation of the variation in phenotypic manifestations in affected females. Some females are minimally affected whereas others may be so severely affected that they die in infancy (Küster and Olbing, 1964).

(ii) Other possible explanations for the pedigree patterns in the Bloch-Sulzberger syndrome include autosomal dominance with sex limitation to the female and lethality in the male, or a cytoplasmic factor which is lethal in males.

(iii) The early stages of the disease resemble an inflammatory reaction in the skin and the finding of eosinophil leucocyte deposits in the skin, liver, and spleen (Küster and Olbing, 1964) suggest that the disease may be due to an infective agent. In fact cytoplasmic inclusions similar to those in molluscum contagiosum have been identified in this disease (Murrell, 1962). If infection occurs *in utero* then possibly susceptibility is genetically determined. In a pair of twins Hitchin and Hall (1964) found that whereas the female twin was affected the male twin was healthy, perhaps because he was not hemizygous (or heterozygous) for the Bloch-Sulzberger gene.

In this report, the proband's mother had a right microphthalmos and was almost completely blind in this eye. There have been several reports of ocular malformations in the relatives of cases with Bloch-Sulzberger syndrome (Scott *et al.*, 1955), and it is possible that in this report the proband's mother was a carrier of the mutant gene. It is difficult to assess the situation with regard to the maternal aunt whose only complaint was of blurred vision in the right eye. If she was affected then the maternal grandmother must also carry the gene, but she showed no manifestations of the disease and had been healthy apart from arthritis. On the present evidence it seems that the maternal aunt was not affected and that the disease in this family was the result of a new mutation in a gamete from one of the maternal grandparents.

Summary

A child with Bloch-Sulzberger syndrome is described. Her mother (and perhaps a maternal aunt) may also be affected to a mild degree. The clinical manifestations and possible mode of inheritance are discussed.

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REFERENCES

- Bardach, M. (1925). Systematisierte Naevusbildungen bei einem eineiigen Zwillingsspaar. Ein Beitrag zur Naevusätiologie. *Z. Kinderheilk.*, **39**, 542.
- Bloch, B. (1926). Eigentümliche, bisher nicht beschriebene Pigmentaffektion (Incontinentia pigmenti). *Schweiz. med. Wschr.*, **7**, 404.
- Butterworth, T., and Streat, L. P. (1962). *Clinical Genodermatology*. Williams and Wilkins, Baltimore.
- Calnan, C. D. (1952). Incontinentia pigmenti (Bloch-Sulzberger). *Brit. J. Derm.*, **64**, 201.
- Carney, R. G. (1951). Incontinentia pigmenti: a report of five cases and review of the literature. *Arch. Derm. Syph. (Chic.)*, **64**, 126.
- Findlay, G. H. (1952). On the pathogenesis of incontinentia pigmenti. With observations on associated eye disturbance resembling retrolental fibroplasia. *Brit. J. Derm.*, **64**, 141.
- Franklin, A. W. (1952). Incontinentia pigmenti; report of a case, with summary of 29 cases from the literature. *Brit. med. J.*, **1**, 75.
- Garrod, A. E. (1906). Peculiar pigmentation of the skin in an infant. *Trans. clin. Soc. Lond.*, **39**, 216.
- Gorlin, R. J., and Anderson, J. A. (1960). The characteristic dentition of incontinentia pigmenti. *J. Pediat.*, **57**, 78.
- Haber, H. (1952). Bloch-Sulzberger syndrome (incontinentia pigmenti). *Brit. J. Derm.*, **64**, 129.
- Hitchin, A. D., and Hall, D. C. (1964). Incontinentia pigmenti (Bloch-Sulzberger syndrome) and its dental manifestations. *Brit. dent. J.*, **116**, 239.
- Jackson R., and Nigam S. (1962). Incontinentia pigmenti: a report of 3 cases in one family. *Pediatrics*, **30**, 433.
- Küster, F. von, and Olbing, H. (1964). Incontinentia pigmenti: Bericht über neun Erkrankungen in einer Familie und einen Obduktions befund. *Ann. paediat. (Basel)*, **202**, 92.
- Lenz, W. (1963). *Medical Genetics*. University of Chicago Press, Chicago.
- Lyon, M. F. (1962). Sex chromatin and gene action in the mammalian X-chromosome. *Amer. J. hum. Genet.*, **14**, 135.
- McKusick, V. A. (1962). On the X chromosome of man. *Quart. Rev. Biol.*, **37**, 69.
- Marty, S. D., Bechtel, H. B., and Wood, C. E. (1958). Incontinentia pigmenti: report of a family. *A.M.A. Arch. Derm.*, **78**, 607.
- Murrell, T. W., Jr. (1962). Personal communication to McKusick (1962).
- Oldfelt, V. (1959). Incontinentia pigmenti. *J. Pediat.*, **54**, 446.
- Rozehnal, V., and Vodička, F. (1957). Incontinentia pigmenti in four girls of the same family. [In Czech.] *Čs. Pediat.*, **12**, 549.
- Scott, J. G., Friedmann, A. I., Chittors, M., and Pepler, W. J. (1955). Ocular changes in the Bloch-Sulzberger syndrome (incontinentia pigmenti). *Brit. J. Ophthalm.*, **39**, 276.
- Sulzberger, M. B. (1927). Über eine bisher nicht beschriebene congenitale Pigmentanomalie (Incontinentia pigmenti). *Arch. Derm. Syph.*, **154**, 19.