STURGE-WEBER'S SYNDROME*

REPORT OF AN UNUSUAL CASE

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No case exhibiting so many interrelated abnormalities as were seen in this patient could be found in the available literature.

Case Report

A man aged 26 was admitted to hospital on October 21, 1954, complaining of failing vision in the right eye. No relevant family history could be obtained and he had had no serious disease before the age of 10 years, when he became ill with fever and skin eruption. While in Persia in 1941, he had been treated for trachoma in both eyes, and at that time the visual acuity of the left eye was so poor that he was unable to read with it. In 1950, pain and aching all over the body were treated by his own doctor, to whom he gave a history of frequent epistaxis since childhood. About Easter, 1951, the visual acuity of the right eye began to deteriorate and he was compelled to give up driving lessons and to leave his work.

On admission to hospital, besides impairment of visual acuity, he also complained of transient slight headache, confined mainly to the occipital region and the back of the neck, which he noticed especially when bending down and after effort.

Examination.—He appeared to be well-built and well-nourished. The lungs, heart, and abdomen showed no gross abnormality. The face was covered with flat patches of naevus flammeus, corresponding roughly with the trigeminal area. Similar patches were seen on the soft and hard palate (which was unusually high), and on the arms and the left side of the chest. The vascular changes were much more pronounced on the left side of the body, especially on the left arm (Fig. 1, opposite). Among the vascular spots there were also whitish areas of depigmentation of the skin, clearly seen on the left side of the chest and the left arm. The anterior incisors were better developed than the lateral ones, and the canines were pointed.

Both eyeballs, especially the left one, showed some degree of proptosis. On both sclerae there were extensive patches of slate-grey pigmentation. Brown flecks were seen at the openings of the canals of the ciliary vessels. The corneae were clear, Descemet's membrane intact, and the anterior chambers quite deep, the left one apparently the deeper.

Both irides were dark brown and showed in their lower parts a marked division by a well-developed iris frill (collarette), which reached the pupil in numerous and dense radial ridges. The upper part of the iris frill seemed to be non-existent, but a more detailed examination showed that it was only less pronounced and displaced towards the pupils, which made the pupillary zone of the iris much narrower. The sphincter design was missing in the upper parts of the irides.

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FIG. 1.—Showing distribution of naevus patches, more pronounced on left side of face and trunk, slight proptosis of left eye, and depigmented areas underneath left nipple and on left arm.

The pupillary margin was of normal shape when seen from below, but from above it appeared as a smooth dark-brown strip without crenations. The pupils were pear-shaped with the stalk in the left eye at about 11 o'clock (Fig. 2), and in the right eye at about 1 o'clock.

FIG. 2.—Pear-shaped pupil of left eye.

Their reaction both to light and to accommodation was very sluggish and confined to the area of the normal iris. The media were clear and transparent.

In the right fundus there was pronounced tumour-like papilloedema of long-standing and about 7D elevation. On the temporal side and above the swollen optic disc, there was a small tortuous angioma-like vessel, terminating in an old haemorrhage. The visual acuity was 6/60. The ocular tension was normal.

In the left fundus there was pronounced cupping (about 5D) of the disc, with advanced optic atrophy. The ocular tension was 40 mm. Hg (Schiötz). The visual acuity was almost 6/60. Transillumination of the eyeballs failed to reveal any abnormal shadows.

Laboratory Investigations.—Urine normal. Blood count normal. X-ray of skull, no major abnormality. No other abnormalities in the central nervous system.

Diagnosis.—The presence of advanced papilloedema suggested the probable existence of a space-occupying cerebral lesion, and, on the advice of Dr. E. R. Bickerstaff, the patient was transferred to the Midland Centre of Neurosurgery. A bilateral arteriogram showed a large temporal tumour.

Operation.—Craniotomy was performed on December 1, 1954, and a very large tumour was discovered in the right temporal lobe, rising from the lateral fissure and surrounded by an area of haemorrhage. Though its appearance was rather odd, it was thought from the way it shelled out to be a meningioma. Section of the tumour, however, showed it to be a melanoma, which was thought to originate in the eye.

Pathological Report on the Tumour and Cyst Walls.—"The specimen consists of a large number of pieces of friable, haemorrhagic tumour. The section shows a typical melanoma, some areas of which are completely amelanotic. No mitoses are to be seen".

Progress.—At first the patient's post-operative condition was good. No abnormal neurological symptoms were found, and gradually the papilloedema of the right eye receded (Fig. 3).

The visual acuity in the right eye deteriorated but slowly recovered. After the initial period, however, the patient showed marked mental disturbance; he later improved considerably but never regained his pre-operative mental condition.

Some weeks after the operation, the papilloedema had subsided and the angioma-like vessel and haemorrhage had disappeared, but the patient began to deteriorate (Fig. 4).

FIG. 3.—Shortly after operation.

FIG. 4.—Showing relapse of brain tumour, butterfly-like distribution of facial naevus, slight proptosis of left eye, and under-developed second incisors.

He first developed swelling of the liver, and then swelling of the skull flap; he became dull and confused, and finally a left hemiparesis appeared, affecting the arm more than

the leg. It was apparent that these symptoms were due to local relapse and to secondary deposits. The patient grew rapidly worse, lost control of sphincters, became semi-conscious, and died on July 27, 1955. Permission for a *post-mortem* examination was not granted.

Discussion

Melanosis of the Sclera.—According to Duke-Elder (1942a), this is not a rare condition. It may progress rapidly in youth and more slowly in age, but often remains more or less stationary. The possibility of a more serious prognosis has to be borne in mind, and the high incidence of malignant change makes it necessary to regard these cases with some anxiety.

Pear-Shaped Pupils.—These are described as extremely rare by Duke-Elder (1942b), who includes them with “pupil anomalies other than colobomata”.

A few cases similar to that described above were reported by Liebitzky (1929), who stated that the main symptoms of this iris anomaly were pear-shaped pupils, simplified structure of the pupillary margin, and local absence of the sphincter.

Whatever the cause of this anomaly, the present case seems to prove that pear-shaped pupils cannot be regarded as a mere variation of an atypical coloboma. The symmetrical structure of the pupils in this case may be due rather to a primary inhibition in development of a sector of the optic cup than to accidental inhibitory effect of a persistent capsulo-pupillary vessel.

Sturge-Weber's Syndrome.—Sturge (1879) described this disease as “congenital glaucoma with coexistent naevus flammeus and epileptiform fits of the opposite side of the body”. He postulated a focal lesion of the cerebrum similar to that found on the face. In Sturge's patient, one pupil became oval in shape with the narrow end downwards after homatropine. Parkes Weber (1929) reported a patient with right-sided hemiatrophy, right-sided congenital spastic hemiplegia, widespread cutaneous vascular naevi with bilateral involvement of the face, and left glaucoma. Skull *x* rays revealed that the left side of the brain was more opaque than the right. No epileptic fits occurred. Weber later succeeded in obtaining radiological evidence of intracranial calcifications, which he regarded as tortuous and calcified blood vessels.

Cerebral and Neural Involvement.—Krabbe (1934, 1955), having performed a biopsy on one of his cases, was able to demonstrate that the calcifications were not confined to the pial vessels but also involved the cerebral cortex. He found angiomatous changes of the pia and focal aplasia of the brain, with probable secondary sclerosis and calcifications of the aplastic area. This developmental defect was thought to be both ectodermal and mesodermal in origin. He suggested that Sturge-Weber's syndrome originated in early foetal life many weeks before the development of the trigeminal nerve, and that the distribution of the naevus vasculosus in the

trigeminal area was merely accidental. The abortive forms could be considered only on the understanding that the disease had no distinct limits. The term Sturge-Weber syndrome should be applied only in cases showing both the naevus on the face and intracranial calcifications of the special type demonstrable on x-ray films.

Kautzky (1949) suggested that the Sturge-Weber syndrome was due to an inborn inhibition of the parasympathetic part of the cerebrospinal nerves, mainly the trigeminal nerve.

Van Bogaert (1950) described the Sturge-Weber syndrome as essentially a cutaneous and meningeal angiomatosis. Although cerebral angiomatosis was found in many cases, the cortical changes were secondary to the mesodermal defect, thus showing an atrophy, not aplasia. He drew attention to the relation between pigment dystrophies and angiomatoses and presumed the existence of neurodermal melanosis although he was unable to find a case wherein the ocular melanosis was associated with meningeal melanosis in the literature.

Calcifications.—According to Livingstone, Eisner, Brown, and Boks (1956), the syndrome has three main features: a vascular naevus, mainly in the trigeminal area, radiological evidence of calcifications, and convulsions. The last appears to be a constant symptom, but the naevus and intracranial calcifications are not always present. In one case, reported by these authors, many x-ray examinations of the skull were made on numerous occasions between the ages of 3 and 18 years, but no evidence of calcification was seen.

It is not yet known how the mineral deposits of iron and calcium occur in the angiomatous and atrophic cortex. Some authors have underlined the role of lipid breakdown and liberation of the phosphoric acid in preparing necrotic tissue for calcification, but much further investigation is necessary to solve this problem. Tingey (1956) reported the results of the chemical analysis of iron and calcium in the brain in three cases of Sturge-Weber's syndrome. A great deal of calcium was present in the white matter as well as in the cortex, but no excess of iron was found.

Frigyer, Mattyus, and Molnar (1953) stated that calcification was the most frequent symptom of the Sturge-Weber syndrome, but was not essential to the diagnosis. The vascular anomaly was the primary change and this explained the circumscribed nature of the clinical picture. The metabolic changes due to the vascular anomaly caused colloid formation, calcification, and destruction of the brain substance. The vessel wall was the primary site of deposition.

Heredity.—According to Bergstrand, Olivecrona, and Tönnis (1936), the Sturge-Weber syndrome was due to a congenital tendency which might be inherited, but there was not such clear evidence of heredity as in von Reck-

linghausen's and von Hippel-Lindau's diseases. The anatomical changes appeared immediately after birth, but grew larger as time went on, the brain and eye changes sometimes appearing later in life.

Related Conditions.—There is a close relationship between the Sturge-Weber syndrome and three other diseases involving vascular changes: those of von Recklinghausen, von Hippel-Lindau, and Bourneville. In von Hippel-Lindau's disease there are angio-reticulomata in the cerebellum, spinal cord, and retina; in Bourneville's disease there are angio-gliomata, renal angiomas, and angioma sebaceum Pringle on the skin; in von Recklinghausen's disease naevi anaemici appear on the skin; in the Sturge-Weber syndrome teleangiectases appear in the cerebellar cortex and choroid, angioma racemosum in the pia, and naevus flammeus on the skin.

Bergstrand and others (1936) also thought that a great number of cases of naevus flammeus over one or more trigeminal branches without any other symptoms were abortive forms of the Sturge-Weber syndrome. The symptoms in less severe cases might interchange in various ways. There was a frequent incidence of naevus flammeus and glaucoma or naevus flammeus with cerebral changes and epileptic fits.

Yakovlev and Guthrie (1931) regarded the vascular malformation as merely the most pronounced symptom of malformation of the brain, the developmental embryonic period at which the malformation began being alone responsible for the development of angiomatosis, neurofibromatosis, or tuberous sclerosis.

All these diseases belong to the so-called phacomatoses (φακωμα = birth mark) or hamartoses (ἀμαρτία = deviation, defect). Cases have been published in which these symptoms appeared together in one patient and were accompanied by other pathological changes. Bergstrand and others (1936) showed the Sturge-Weber syndrome to be associated with meningioma in one case, and with acromegaly in another.

Neural debility, obesity, sexual infantilism, highly arched palate, abnormally developed ears, flattened nasal base, and malformed teeth (better developed anterior incisors, undeveloped lateral incisors, pointed canines) have been described, as well as lesions more frequently found in tuberous scleroma and neurofibromatosis, such as cysts, congenital tumours of the viscera, etc.

Nonnenmacher (1955) published a report of a patient with Sturge-Weber's syndrome who simultaneously exhibited symptoms of Klippel-Trenaunay's (Parkes Weber) disease. A flat naevus vasculosus was scattered all over the body, especially on the face and arms, and more on the right than on the left side, capillary ectases appeared on the soft and hard palate, and there was bilateral buphthalmos, but calcifications were not found, and there were no epileptic fits. The flat naevus vasculosus and osteohypertrophy of the right side of the face and the right leg are typical of the Klippel-Trenaunay

syndrome. The same author included the neurodermal melanosis of Touraine (1949) among the phacomatoses.

Epileptic Fits.—According to Parnitzke (1956), the complete picture of the Sturge-Weber syndrome is characterized by facial naevus flammeus, congenital or acquired glaucoma, local or general convulsions, and calcified cerebral angiomas. Classic cases with fully-developed symptoms are infrequent but many authors state that at least two symptoms must be present to establish a diagnosis of Sturge-Weber disease. Parnitzke described four cases ranging from the fully-developed picture to a single symptom. The most interesting is his Case 4 in which only the typical, symmetrical intracranial calcifications were found; naevus, glaucoma, epileptic fits, and dementia were not present, but the patient had attacks of migraine.

Epileptic attacks occur only in patients with an inherent predisposition for convulsions. In some cases the calcifications are undetectable by radiological examination and can be found only by microscopy. Epileptic fits occur in the majority of cases, but Parnitzke's Case 4 seems to prove that the statistical data are artificial, because usually it is only the patients with epileptic fits who come to our notice. In such cases the epileptic fits appear much later in life and other abnormal neurological symptoms are absent.

Glaucoma.—The most important ocular complication of the Sturge-Weber syndrome is congenital or acquired early glaucoma, which does not necessarily occur on the same side as the naevus flammeus. Histological examination reveals angiomatous changes in the choroid. Various authors have reported optic atrophy; strabismus; angiomatous changes of the conjunctiva, sclera, iris, ciliary body, and retina; retinal glioma; choroidal atrophy; strands of persistent pupillary membrane; heterochromia of the irides; and exophthalmos. Inigo (1952) added posterior capsular cataract, and described a case which showed widespread angiomas of the conjunctiva and sclera with enlarged and tortuous vessels, multiple small angiomatous changes in the iris, luxation of the lens into the anterior chamber, and total detachment of the retina.

Although there is no clear evidence of heredity, there is general agreement that an hereditary tendency is often present. Werner (1952) thought that in the Sturge-Weber syndrome as in other phacomatoses an inherited weakness of the germinative plasma is responsible for a developmental inhibition of the as yet undifferentiated neuro-epithelial cells, with subsequent damage to the skin and nervous system; there is certainly also a disturbance of the mesodermal structures. The inhibitory factor is unknown, but Werner mentions rubella embryopathy, and suggests that the various phacomatoses depend on the manner and scope of the inhibition, on the time of its action, and on the degree of inherited tendency. King and Schwarz (1954) also favoured embryonic maldevelopment, and quoted Sabin (1917) and Streeter

(1918), who postulated a developmental vascular inhibition as the causative factor.

Bock (1950) reported an unusual case of the Sturge-Weber syndrome in a child with bilateral glaucoma, haemangioma of the face and forehead, cerebral changes, and epileptic fits. The ocular tension rose after massage but was little influenced by homatropine.

It is not clear how the glaucoma arises. The abnormal condition of the choroidal vessels and frequent presence of angiomas and intra-ocular capillary dilatations lead to venous stasis and disorganization of the circulation of fluid. Deficient drainage, such as is found in buphthalmos without naevus flammeus, and developmental anomalies (*e.g.* absence of the canal of Schlemm) may also play a part. Duke-Elder (1954) wrote that, although glaucoma-like naevus is congenital and buphthalmic in type, cases of simple, chronic glaucoma without deformation of the globe do occur. This glaucoma is often chronic and non-inflammatory, associated with deeply cupped and atrophic discs and progressing to complete blindness, though many patients may keep their sight for a long period despite increased ocular tension.

As the site of the brain changes is far removed from the motor region, the epileptic fits are probably due to the consecutive shrinkage of the grey matter. The angiomatous appearance of the cerebral vessels is frequently seen in younger patients, and the atrophy and calcifications in those of more advanced years, although pronounced calcifications have been found in a child aged 14 months, and no calcium shadows in a man aged 45. The oldest case recorded seems to be that of Frigyer and others (1953). A man aged 63 had naevus vasculosus on the left side of the face, glaucoma of the left eye, right-sided spastic hemiparesis, epileptic fits, and mental debility.

My patient displayed symptoms of incomplete Sturge-Weber syndrome, with widespread naevus flammeus, more pronounced on the left side of the face and trunk, and left-sided glaucoma with proptosis. As no *post-mortem* examination was made, nothing can be said about the condition of the cerebrum.

Cerebral Melanoma.—The combination of Sturge-Weber's disease with melanoma of the brain has not, to my knowledge, been reported before. The melanoma in the case described above was thought by one neuro-surgeon to have originated in the eye, but this suggestion could not be proved because no *post-mortem* examination was carried out. It may even have originated in an insignificant overlooked lesion of the skin, especially since the patient had been suffering from widespread disturbance of the cutaneous pigment. Any atypical or bizarre malignant skin neoplasm may be a malignant melanoma. Allen (1949) pointed to the presence of clusters of altered cells in malignant pigmentation, and Cade (1957) has stressed the importance of this point in diagnosis.

No such alterations were found, however, in the histological examination of my patient. In his case the melanoma could have developed independently

of either the eye or the skin, from pigmentary changes in the meninges themselves. Neither eye showed, until his death, the slightest evidence of being affected by primary melanoma. No cutaneous naevus pigmentosus was seen. Both local relapse and metastasis to the liver started some months after the operation on the brain tumour, which suggests that the secondary deposits originated in that tumour.

Touraine (1949) regarded the tendency to metastasis as one of the features common to both cutaneous melanomata and those of the central nervous system (Pol, 1905; Boit, 1907; Ehnmark and Jacobowsky, 1926; Baumecker, 1929; Foot and Zeek, 1931, Case 2). He considered that malignant melanomata usually developed from naevi pigmentosi or from precancerous melanosis, but might also originate in an apparently normal skin. This also applied to malignant melanomata of the meninges, which might develop from melanism or melanotic patches, but also in a tissue, normal in appearance, containing disseminated melanocytes. He regarded the melanogenesis and the subsequent pigmentation as a normal process of ectodermal origin, common to the skin, some mucous membranes, and the soft meninges.

Willis (1952) thought that interpretation of the origin of the growth was open to grave doubts, unless the cases reported by Hassin and Bassoe (1929) and Foot and Zeek (1931, Case 2), in which metastatic melanotic growths accompanied the allegedly primary melanotic tumours of the meninges or nervous system, were accepted. However, there is no intrinsic reason why malignant melanomata of the brain should not give rise to metastases, although so far no indisputable examples of this occurrence have been noted, and a critical study of such cases, including careful necropsy, is necessary.

As no adequate investigations were carried out in the case described above, and the *post-mortem* findings are lacking, each of the theories regarding the origin of the brain melanoma put forward has its merits and defects, and none can be either fully approved or completely discarded. The most acceptable is that of the simultaneous coexistence of various melanotic anomalies due to generalized pigment disturbance. As far as the melanotic changes are concerned, it appears to me that my patient's symptoms might be regarded as a supplementary extension to Touraine's original description of *melanose neurodermale*, presenting instead of cutaneous melanosis, amelanotic changes in the skin, melanoma of the brain (parts of which were entirely amelanotic), and also melanosis of the sclerae. On admission, the case was thought to be a link between Sturge-Weber's and von Hippel-Lindau's syndromes, on account of the angioma-like vessel in the right fundus. In the light of the evidence, it should rather be considered as a link between Sturge-Weber's syndrome and Touraine's *melanose neurodermale*.

Summary

A case is presented in which glaucoma of the left eye was combined with naevus flammeus of the face and trunk and generalized disturbance in

pigment distribution, culminating in the development of a brain melanoma.

Pear-shaped pupils, high-arched palate, and dental abnormalities were secondary features.

The case may be regarded as an incompleated example of Sturge-Weber's syndrome coexistent with the melanotic dysplasia described by Touraine as *melanose neurodermale*.

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