Von Hippel's disease in association with von Recklinghausen's neurofibromatosis

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SUMMARY Ten members of a large family who showed manifestations of either von Hippel-Lindau disease or von Recklinghausen's neurofibromatosis were examined. Three of 10 members were found to have retinal angiomas which had not been present on fundus examination 3 years previously. These angiomas were associated with ocular and systemic signs of neurofibromatosis. These cases show overlapping manifestations of different phakomatoses and provide support for the concept of a common aetiology for these diseases.

In 1923 Van der Hoeve introduced the term 'phakomatoses' to describe a heredofamilial group of diseases characterised by the presence of disseminated hamartomas (Van der Hoeve, 1923). The 6 diseases that constitute this group are tuberous sclerosis or Bourneville's disease, von Recklinghausen's neurofibromatosis, von Hippel-Lindau disease, meningocutaneous angiomatosis or Sturge-Weber syndrome, ataxia-telangiectasia or Louis-Bar syndrome, and arteriovenous communication of retina and brain or Wyburn-Mason syndrome (Yanoff and Fine, 1975). The term von Hippel's disease refers to retinal angiomatosis not occurring in association with a vascular tumour of the central nervous system. Similarities in inheritance patterns and affected germ layers have been noted among the phakomatoses. However, each has distinctive clinical features, and reports of overlapping manifestations of 2 phakomatoses in the same individual or family are uncommon (Fracassi and Parachu, 1935; Chapman *et al.*, 1959; Melmon and Rosen, 1964).

The present report adds 3 new cases of von Hippel's disease from a large family (Fig. 1) with known overlapping signs of von Hippel-Lindau disease and von Recklinghausen's neurofibromatosis.

Case reports

CASE 1

(Subject IV-17 in Fig. 1). A 17-year-old woman was admitted to a hospital at the age of 13 for evaluation

of severe headaches and projectile vomiting. Physical examination at that time showed a normal blood pressure, numerous large café-au-lait spots, and axillary freckles. Cutaneous neurofibromas were not present. Ocular examination showed normal retinal vasculature in both fundi. Family history revealed that her mother had overlapping manifestations of Lindau's disease and von Recklinghausen's neurofibromatosis proved at necropsy. A pneumoencephalogram and ventriculogram showed hydrocephalus with aqueductal stenosis and a mass in the thalamic area on the left side. Owing to her skin lesions and the family history of neurofibromatosis the thalamic mass was thought to be a glioma, though a tissue diagnosis was not made. Radiation therapy was begun at this time. The patient's hospital course was complicated by meningitis, malfunctioning shunts, and paraplegia secondary to arachnoiditis.

At age 14 years ophthalmoscopic examination revealed a visual acuity of RE 10/30 and LE 12/30. The fundi were normal except for resolving papilloedema of the left optic disc. Two years after onset of symptoms the patient had marked limitation of intellectual and motor functions.

In March 1977 the patient was referred to the Massachusetts Eye and Ear Infirmary for evaluation of a 'greenish mass' in the left eye. Ocular examination showed a visual acuity of RE 20/50 and LE hand motions at 1 ft (30 cm). Forty-five prism dioptres of left exotropia and a Gunn pupillary reaction in the left eye were present. Slit-lamp examination revealed multiple iris naevi in both eyes. Fundus examination of the right eye showed retinal angiomas in 3 areas (Figs. 2, 3, 4). A non-rhegmatogenous retinal detachment sparing the

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macular area was present in both inferior quadrants and in the superonasal quadrant. Considerable vitreous membrane formation was present overlying the angiomas in the superonasal quadrant (Fig. 2).

Fundus examination of the left eye showed a long-standing total retinal detachment partially obscured by old vitreous haemorrhage. A red mass seen in the superonasal quadrant was thought to be a retinal angioma. The patient was admitted to hospital for surgical treatment of retinal detachment, and a preoperative neurological evaluation, including computerised axial tomography (CAT) scan, revealed a large left thalamic mass which was consistent with the diagnosis of thalamic glioma.

Cryotherapy of the retinal angiomas combined with scleral buckling was successfully performed on the right eye.

A shave skin biopsy of a café-au-lait spot from the left arm was obtained (Fig. 5) and sent for electron microscopic examination in order to establish a tissue diagnosis of von Recklinghausen's neurofibromatosis. This showed macromelanosomes in melanocytes of the epidermis (Fig. 6).

CASE 2

(Subject IV-18 in Fig. 1). A 14-year-old boy was examined 3 years before the present examination, at which time signs of neurofibromatosis were found, while both fundi appeared normal. CAT-scan examination 2 months previously was negative for intracranial lesions. The patient complained of occasional headaches but denied other neurological symptoms. He had no symptoms referable to his kidneys, adrenal glands, pancreas, or thyroid

gland. His blood pressure was 130/80 mmHg. Examination of his skin showed more than 6 café-au-lait spots. One subcutaneous nodule was present on the right leg.

Ocular examination showed that the visual acuity was 20/25 in both eyes. Applanation tensions were 15 mmHg in the right eye and 19 mmHg in the left. On biomicroscopy numerous iris naevi were seen, and fundus examination showed retinal angiomas in both eyes (Figs. 7, 8).

CASE 3

(Subject IV-16 in Fig. 1). A 20-year-old woman was examined 3 years previously and was found to have signs of neurofibromatosis and normal ocular fundi. The patient complained of occasional headaches but denied other neurological symptoms. Her blood pressure was 158/84 mmHg. Examination of her skin showed 3 café-au-lait spots measuring greater than 1.5 cm each. Multiple small cutaneous neurofibromas were noted.

Ocular examination revealed a visual acuity of RE 20/20 and LE 20/25. Intraocular pressure by applanation tonometry was 21 mmHg in the right eye and 16 mmHg in the left eye. Slit-lamp examination showed numerous iris naevi. Ophthalmoscopy revealed a retinal angioma in the superonasal quadrant of the fundus of the right eye. The left fundus was within normal limits.

Discussion

The phakomatoses are syndromes of hereditary origin; all except the Louis-Bar syndrome are

Fig. 1 Pedigree of a family, certain members of which have von Recklinghausen's neurofibromatosis, von Hippel-Lindau disease, or a combined syndrome (reprinted from *Neurology*, 25, 840-4, with permission from Dr P. Tishler)

Fig. 2 Retinal angiomas with dilated vessels and overlapping membranes in superonasal quadrant of right eye in Case 1

Fig. 3 Retinal angioma in inferotemporal quadrant of right eye in Case 1

Fig. 4 Retinal angioma in inferonasal quadrant of right eye in Case 1

Fig. 5 Typical café-au-lait spot in von Recklinghausen's neurofibromatosis from Case 1

Fig. 7 Retinal angioma in inferior portion of fundus of right eye in Case 2

Fig. 8 Retinal angioma in inferotemporal quadrant of fundus of left eye in Case 2

Fig. 6 Electron micrograph of skin biopsy of café-au-lait spot in Case 1. Macromelanosomes (MM) in melanocyte (MEL) in epidermis are seen. Adjacent epidermal cells (E) containing melanosomes of normal size (NM) are present. Basement membrane separates epidermis from underlying dermis (original magnification $\times 16\,000$)

transmitted in an autosomal dominant fashion. They are known to have individually characteristic clinical and pathological features which have been well described (Boder and Sedgwick, 1958; Alexander and Norman, 1960; Melmon and Rosen, 1964; Harley and Grover, 1970; Font and Ferry, 1972; Brown *et al.*, 1973). The clinical features of each phakomatosis reflect the abnormal development of predominantly 1 germ layer. Von Recklinghausen's neurofibromatosis and tuberous sclerosis may be considered to be mainly ectodermal abnormalities, while von Hippel-Lindau disease, Sturge-Weber syndrome, Louis-Bar syndrome, and Wyburn-Mason syndrome are characterised by abnormalities chiefly of mesoderm. It has been suggested that the phakomatoses are of embryodysplastic origin and that they show evidence of developmental errors in neuroectoderm and mesoderm, possibly at different stages of development (Waardenburg *et al.*, 1963). Cases in which clinical manifestations of two phakomatoses overlap in the same individual or family are of interest because they support the concept of a common aetiology for this entire group of disorders.

In a previous report of this family (Tishler, 1975) certain members were noted to have von Recklinghausen's neurofibromatosis while others had von Hippel-Lindau's disease. Only one individual had a combined syndrome (neurofibromatosis, café-au-lait spots, pheochromocytomas, cerebellar haemangioblastoma, renal cell carcinoma, and pancreatic cysts). Re-examination of 10 members of this family showed retinal angiomas associated with von Recklinghausen's neurofibromatosis in 3 members. We found only 2 other patients with

neurofibromatosis and retinal angiomas in the ophthalmic literature (Frenkel, 1967; Wolter, 1965). In the latter case the angiomas were solitary.

Von Recklinghausen's neurofibromatosis is known to involve the skin, nervous system, bones, endocrine glands, and eyes. The most striking clinical expression of the disease is the presence of café-au-lait spots. 80% of patients with neurofibromatosis can be diagnosed by the presence of more than six café-au-lait spots. From the remaining 20% those over 21 years of age will usually have multiple cutaneous tumours and few pigmented spots, while those under 21 years may have no dermal tumours and few pigmented spots (Adams and Reed, 1971). It is known that 10% of the normal population have 1 or more café-au-lait spots, and these pigmented skin lesions have also been reported in Albright's syndrome, a condition closely related to neurofibromatosis. Electron microscopic observations indicate that macromelanosomes are present in melanocytes in the café-au-lait spots of von Recklinghausen's neurofibromatosis (Jimbow *et al.*, 1973) but are absent in the café-au-lait spots of normal subjects (Johnson and Charneco, 1970) and in patients with Albright's syndrome (Benedict *et al.*, 1968).

Since in Case 1 the diagnosis of von Recklinghausen's neurofibromatosis was not confirmed by tissue diagnosis of the suspected thalamic glioma, a skin biopsy of a café-au-lait spot was performed. Electron microscopic examination of the biopsy specimen revealed macromelanosomes in melanocytes in the epidermis, thus confirming the diagnosis of neurofibromatosis.

The findings in von Hippel-Lindau disease include

haemangioblastomas of the retina, cerebellum, medulla, and spinal cord, pancreatic cysts, renal cysts, hypernephromas, and rarely phaeochromocytomas. A clinical feature common to both diseases is the presence of phaeochromocytomas. These adrenal gland tumours are found in approximately 10% patients with neurofibromatosis, while they have been reported in only 9 cases in association with von Hippel-Lindau disease (Wise and Gibson, 1971).

Associations between the other phakomatoses have been previously described. Glial hamartomas of the retina and optic nerve head are known to occur in both von Recklinghausen's neurofibromatosis and tuberous sclerosis (Van der Hoeve, 1932). Neurofibromatosis has been reported in patients with tuberous sclerosis and in members of the same family (Kirby, 1951). Two coexisting conditions—tuberous sclerosis and a large vascular malformation over the left cerebral hemisphere—in 1 patient provide further evidence of association between phakomatoses (Chapman *et al.*, 1959). In addition adenoma sebaceum and Sturge-Weber syndrome have been reported to occur together in a father and his son (Frenkel, 1967). Tuberous sclerosis has been observed in the uncle of 2 siblings with Lindau's disease (Moller, 1952). Pancreatic cysts, kidney cysts, and hypernephromas are visceral manifestations common to both tuberous sclerosis and von Hippel-Lindau disease (Chapman *et al.*, 1959). The typical cavernous haemangioma or telangiectasis of the facial skin seen in Sturge-Weber syndrome has been described in a patient with Lindau's disease (Font and Ferry, 1972).

It is evident that such associations do exist and their total expression may not be evident during a preliminary examination. Although retinal angiomas are most frequently seen in early life, they may first appear in older individuals. Repeated ocular examinations of these patients are indicated in order to detect the vascular tumours at an early stage when complications have not yet developed and the management is relatively easy.

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