Tuberous sclerosis and Klippel-Trenaunay-Weber syndromes

Association of two complete phakomatoses in a single individual

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SYNOPSIS Tuberous sclerosis and Klippel-Trenaunay-Weber (KTW) syndromes are phakomatoses which are believed to be inherited separately. A 41 year old woman presented with the classic features of tuberous sclerosis: adenoma sebaceum, mental retardation, and seizures. In addition, the diagnostic triad of KTW involved the left lower limb: cutaneous naevi, a vascular anomaly, and osteo-hypertrophy. Arteriography documented the presence of visceral tumours and an arteriovenous malformation of the leg. This is the first reported association of the fully-developed symptomatology of tuberous sclerosis and KTW in one person.

The phakomatoses are a group of inherited disorders characterized by hamartomatous involvement of multiple organ systems (Francois, 1972). The diseases may be broadly classified as primarily either neuroectodermal or mesodermal (vascular) in nature. Although the phakomatoses are believed to be inherited independently, several incomplete forms may be associated in one person (Francois, 1972) or in a family (Schull and Crowe, 1953). However, as stated by Francois, 'virtually no case has so far been found in which the chief symptoms of the phakomatosis were seen together with the characteristic symptoms of another type of phakomatosis'. We describe a patient with the complete symptomatology of both tuberous sclerosis and Klippel-Trenaunay-Weber (KTW) syndromes which we believe is the first reported association of these specific entities.

CASE HISTORY

The patient is a 41 year old mentally retarded black woman who was admitted because of a history of increased difficulty in walking for one year. She

reportedly developed normally until aged 3 years when generalized seizures began and she was noted to be mentally retarded. During early childhood small papular skin lesions appeared on her face and her left leg began to enlarge disproportionately. The patient had progressive difficulty in walking and developed a moderate scoliosis. Her mother and brother had similar facial lesions; the mother remained asymptomatic, but the brother, who also had convulsions and severe retardation died at the age of 17 years.

Physical examination revealed a severely retarded, thin woman who did not speak, but understood simple commands. While in bed she maintained a flexed posture of trunk and extremities, but was able to walk with assistance. Small raised discrete skin lesions characteristic of adenoma sebaceum were present in a 'butterfly' distribution over the nose and malar region as well as on the chin (Fig. 1). A shagreen patch 10×15 cm covered the posterior aspect of the right thigh. Many small nodules were superimposed on diffusely hypertrophic gums. Multiple peri- and subungual fibromas were evident on the fingers and toes. Bony enlargement and firm soft tissue hypertrophy below the left knee including the ankle and foot were striking. Superficial venous varicosities were apparent over the left leg (Fig. 2). One of several flat cutaneous naevi scattered over the hypertrophied leg was biopsied, and demon-

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FIG. 1 *Adenoma sebaceum in the typical 'butterfly' distribution.*

FIG. 2 *The left leg below the knee is markedly hypertrophied. Engorged superficial varices and cutaneous naevi are present.*

strated a capillary haemangioma. Indirect ophthalmoscopy disclosed three grey-white retinal hamartomas less than a disc diameter in size, superior and inferior to the left macula (Fig. 3). Diffuse hyperreflexia was present as well as a prominent jaw jerk, snout reflex and bilateral extensor plantar responses.

Laboratory studies including serum electrolytes,

FIG. 3 *Left fundus, temporal to the disc, showing two hamartomas (arrows) superior to the macula. The central circular reflex is an artefact.*

glucose, blood urea nitrogen, cholesterol, total protein, LDH and aspartate aminotransferase were within normal limits. Urine analysis, complete blood count, brain scan, and spinal fluid examination were normal. An electroencephalogram showed diffuse symmetrical slowing with paroxysmal abnormalities. Radiographs of the skull revealed several sclerotic areas of the calvarium without intraparenchymal calcification. Radiographs of the

1935) compared the oxygen saturation of the femoral veins, showing on the left a PvO_2 of 8.4 kPa with a 93.2% O_2 saturation, and on the right a PvO_2 of 4.4 kPa and a 68% O_2 saturation. Transfemoral arteriography delineated several avascular mass lesions in the liver, spleen, and kidneys, as well as a large arteriovenous malformation in the lower left leg.

COMMENT

Tuberous sclerosis is diagnosed by the combination of adenoma sebaceum, mental retardation, and epilepsy (Critchley and Earl, 1932; Lagos and Gomez, 1967; Donegani *et al.*, 1972), although some authors feel adenoma sebaceum alone is sufficient for diagnosis (Critchley and Earl, 1932). Other synonyms for the disorder include Bourneville's disease (Bourneville, 1880), epiloia (Sherlock, 1911), and neurinomatosis centralis. Associated abnormalities often present are retinal and visceral tumours, shagreen patches, and depigmented skin regions (Gold and Freeman, 1965).

The Klippel-Trenaunay-Weber syndrome (Klippel and Trenaunay, 1900), also known as naevus varicosus osteohypertrophicus, angiomatosis osteohypertrophica, and Parkes-Weber-Klippel syndrome (Kramer, 1972), is a primary mesodermal phakomatosis diagnosed by the triad of: (1) cutaneous naevi, usually on the affected limb; (2) a vascular anomaly of one limb; and (3) osteohypertrophy, often including the entire limb on the side of the vascular malformation. The vascular naevi are primarily ipsilateral to the hypertrophic limb, as in the present case. Flat pigmented naevi which usually follow a radicular pattern may, however, occur on the opposite side and rarely on all four limbs. The vascular anomaly originally described (Klippel and Trenaunay, 1900) was believed to be entirely venous, but Weber (1907, 1918) described arteriovenous vascular anomalies in the affected limb. The high oxygen content in the left femoral vein documented the major degree of arteriovenous shunting in the present patient. While some authors (Lindenauer, 1965) prefer to define two entities dependent upon whether an arteriovenous fistula or only venous varicosities are present, most recent authors agree that a nosological distinction is unwarranted (Mullins *et al.*, 1962; Bereston and Roberts, 1965;

FIG. 4 Radiograph of left leg showing soft tissue hypertrophy, generalized demineralization, and subperiosteal bone formation especially in the lower fibula.

lower extremities demonstrated diffuse soft tissue enlargement in the left leg, generalized demineralization of the left tibia and fibula, and hypertrophic periosteal bone formation (Fig. 4). Pneumoencephalography outlined several deformities in the roof of both lateral ventricles. Brown's test (Horton,

TABLE
CHARACTERISTICS OF TUBEROUS SCLEROSIS, KLIPPEL-TRENAUNAY-WEBER (KTW) SYNDROME, AND PRESENT CASE

<i>Tuberous sclerosis</i>	<i>KTW syndrome</i>	<i>Present report (combined syndromes)</i>
Central nervous system		
Seizures		Seizures
Mental retardation		Severe mental retardation
Ependymal tumours		Irregular ventricular masses on air study
Cerebral tumours		
Hamartomas		
Heterotopias		
Skin and soft tissue		
Adenoma sebaceum		Adenoma sebaceum
Naevi	Cutaneous naevi	Cutaneous naevi
	Venous or arterio-venous anomaly with soft tissue hypertrophy	Arteriovenous malformation
		Soft tissue hypertrophy
Shagreen patches		Shagreen patch
Subungual fibromas		Subungual fibromas
Bones		
Skull defects	Osseous hypertrophy of limb	Left leg osseous hypertrophy
Eye		
Optic disc and retinal hamartomas		Retinal hamartoma
Visceral tumours		
Heart, kidney, uterus, liver, spleen, etc.		Avascular masses in kidney, liver, spleen, and uterine fibroid

Brooksaler, 1966; Owens *et al.*, 1973). Additional symptomatology which may be present in the KTW syndrome includes skin abnormalities such as ichthyosis, hyperhydrosis, and lymphoedema; orbitofrontal varices (Rathbun *et al.*, 1970); pulmonary vein varicosities (Owens *et al.*, 1973); and congenital anomalies such as syndactyly and spina bifida.

The diagnostic and associated features of tuberous sclerosis and KTW syndromes as well as the symptomatology of the present case are outlined in the Table. All the major characteristics necessary for the diagnosis of both syndromes are present in this case. The KTW syndrome has been associated in rare instances with forms of Sturge-Weber disease (Haberland and Perou, 1966; Owens *et al.*, 1973), and Sturge-Weber disease has been accompanied by hemifacial hypertrophy and rarely by vascular anomalies of the limb (Kramer, 1972). Focal or

partial limb gigantism has also been described without varicosities or angiomas (Laxenaire, 1961) and very rarely in patients with von Recklinghausen's disease (Kramer, 1972). Partial limb hypertrophy was associated with adenoma sebaceum in a case alluded to by Louis-Bar and Legros (1947), but no description of the patient was provided.

The phakomatoses are clearly believed to be inherited on separate genes (Borberg, 1951; Schull and Crowe, 1953; Waardenburg, 1963). The incidence of tuberous sclerosis is reported as approximately 1/20 000 to 1/50 000 individuals (Paulson and Lyle, 1966; Zaremba, 1968), while KTW is believed to be even more uncommon (Kramer, 1972). Therefore, cases, as in the present report, with the fully developed complement of two uncommon disorders, will be extremely rare.

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