SCOLIOSIS WITH PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA
IN FOUR SIBLINGS

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In this paper I present a previously undescribed syndrome, characterised by progressive scoliosis and progressive external ophthalmoplegia, occurring in four members of a "sibship" of eleven (Fig. 1). Ocular defects may occur in association with scoliosis in various syndromes, including Marfan's syndrome, homocysteinuria, osteogenesis imperfecta and Ehlers-Danlos syndrome, but scoliosis has not been recorded with progressive external ophthalmoplegia, a disorder in which there is a progressive paralysis of the external ocular musculature.

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FIG. 1
Family tree.

CLINICAL MATERIAL

A Chinese family living in Jamaica was extensively investigated after four siblings, one girl and three boys, had been treated at the University Hospital. Six other siblings, four males and two females, and both parents, were without stigmata of either condition. The eleventh sibling had died at the age of three months. Other relatives were not examined, but the family was not aware of any other relative who suffered from either condition. There was no history of consanguinity.
CASE REPORTS

Case 1—A boy, born in 1944, was brought to the orthopaedic clinic at the age of eleven with a five years' history of progressive back deformity. At this stage he had a left thoracic scoliosis of 70 degrees. Two years later he was admitted to hospital, and after correction in a Risser hinged plaster jacket the spine was fused from the fourth thoracic to the first lumbar vertebra. This operation gave only slight improvement, from 80 degrees to 70 degrees.

He was first noted to have ophthalmoplegia at the age of fourteen, and at twenty-four the developed a habit spasm of the left side of the face.

Physical examination at twenty-six years of age showed severe left thoracic scoliosis (Fig. 2). He was of normal intelligence, with normal sexual development. There was no evidence of weakness of the trunk or limb muscles and deep tendon reflexes were normal. All modalities of sensibility were intact. There was significant joint hypermobility, it being possible passively to hyperextend the fingers to lie parallel with the back of the forearm. The thumb could be passively opposed to the flexor aspect of the forearm and the elbows could be hyperextended more than 10 degrees.

Examination of the eyes revealed bilateral complete paralysis of horizontal deviation of both eyes, but he retained partial vertical movements (Fig. 3). There was bilateral ptosis and he had a fine pendular nystagmus. The pupils were round and reacted to direct and indirect stimulation. Both optic fundi were normal and there was no retinal pigmentation. The visual fields were normal. He had a left-sided facial habit spasm. The remaining cranial nerves were normal.

Case 2—A boy, born in 1947, was brought to the orthopaedic clinic at the age of eight with a marked right thoracic scoliosis which had been first noticed five years previously. The curve measured 50 degrees when he came and deteriorated to 130 degrees in ten years. Although he initially refused operation he consented when he was nineteen: spinal fusion from the third thoracic to the second lumbar vertebra was combined with correction by Harrington instruments. The curve was reduced to 105 degrees. His ophthalmoplegia was noted when he was first seen.

Physical examination when he was aged twenty-three revealed a marked right thoracic scoliosis. He was of normal intelligence with normal sexual development. There was no neuromuscular abnormality in trunk or limbs. There was no joint hypermobility.

Examination of the eyes revealed bilateral complete paralysis of horizontal deviation but he retained partial vertical movements. He was myopic and had bilateral ptosis. There was no nystagmus. Pupils were round and reacted to direct and indirect stimulation. Both optic fundi were normal and there was no retinal pigmentation. The visual fields were normal.

Case 3—A girl, born in 1951, was brought to the orthopaedic clinic at the age of twelve with right thoracic scoliosis of 110 degrees. The curve progressed to 135 degrees by the age of fourteen (Fig. 4), when she underwent spinal fusion from the first thoracic to the second
lumbar vertebra, with Harrington's instrumentation. Since operation the curve has remained at 80 degrees (Fig. 5). Her parents noted that she was unable to move her eyes fully when she was eleven.

At the age of nineteen she had a right thoracic scoliosis. She was of normal intelligence with normal sexual development. There was no evidence of neuromuscular abnormality in trunk or limbs. There was no joint hypermobility.

Examination of the eyes revealed bilateral complete paralysis of horizontal deviation but she retained partial vertical movements. She was myopic and had bilateral ptosis. There was a fine pendular nystagmus. The pupils were round and reacted to direct and indirect stimulation. Ophthalmoscopy revealed normal fundi in each eye with no retinal pigmentation. The visual fields were normal.

Case 4—A boy, born in 1959, came to the orthopaedic clinic at the age of four with his sister (Case 3). An initially mild right thoracic scoliosis increased to 53 degrees by the age of nine.
He was then fitted with a Milwaukee brace which he has been wearing ever since. When first seen his eyes were normal but he gradually developed ophthalmoplegia and ptosis.

At the age of ten he had right thoracic scoliosis. He was of normal intelligence with normal prepubertal development. There was no neuromuscular abnormality in trunk or limbs. His joints showed significant hypermobility.

Examination of the eyes revealed a complete paralysis of horizontal deviation but full vertical movement. There was bilateral ptosis and he had a fine pendular nystagmus. The pupils were round and reacted to direct and indirect stimulation. Ophthalmoscopy revealed normal fundi with no retinal pigmentation. The visual fields were normal.

**INVESTIGATIONS**

The following laboratory results were within normal limits in all four patients: urine analysis for reducing substances, phenyl pyruvic acid, ketones and ketoacids, porphobilinogen, protein; twenty-four-hour urinary calcium and aminoacid analysis; blood urea, serum electrolytes, calcium, phosphorus, alkaline phosphatase, transaminases, plasma protein electrophoresis, plasma aminoacid analysis; electrocardiograph. All four patients had asymptomatic \( \alpha \), thalassaemia, \( \beta \) thalassaemia. All other members of the family have mixtures or combinations of \( \alpha_1 \), \( \alpha_2 \) and \( \beta \) thalassaemia. Thalassaemia is common in Chinese Jamaicans, and it was not thought to be related to the syndrome described here.

**DISCUSSION**

The genetics of idiopathic scoliosis are not fully understood. There have been a number of reported cases of a familial incidence. Garland (1934) described a family with nine affected members in five generations. There have been several reports of both identical and non-identical twins being affected.
Wynne-Davies (1968) in a study of the relatives of 114 patients with idiopathic scoliosis deduced that idiopathic scoliosis is familial and is caused by dominant or multiple gene inheritance. De George and Fisher (1967) in a postal study of the families of 446 patients concluded that inheritance does not fit with either dominant or recessive patterns, and is probably multi-factorial. High concordance in monozygotic and dizygotic twins suggested maternal influences in utero. Cowell, Hall and MacEwen (1969) suggested that family members were much more commonly affected on radiological criteria, and postulated a sex-linked dominant inheritance with variable expressivity and incomplete penetrance.

Ophthalmoplegia occurs in a number of conditions including diabetes, disseminated sclerosis, myasthenia, aneurysms and endocrine abnormalities. The syndrome of progressive external ophthalmoplegia is well documented by Drachman (1968), who examined the various abnormalities that have been reported in association with it. No association with scoliosis is mentioned. About half the cases of progressive external ophthalmoplegia reported so far have a genetic association. It is not known whether the defect is myopathic or neuropathic. Progressive external ophthalmoplegia may occur with a variety of other dysplasias, including peripheral muscle weakness, heart block and retinitis pigmentosa.

Acanthocytosis may present with progressive external ophthalmoplegia and nystagmus and peripheral muscle weakness. There is an associated absence of beta lipoprotein. The defects in Refsum’s disease may include progressive external ophthalmoplegia, nystagmus, cerebral ataxia and retinitis pigmentosa, associated with an excess of serum phytanic acid.

Ocular defects have been noticed with scoliosis and indeed scoliosis may be secondary to unilateral ophthalmoplegia (Dietrich 1967). Ponseti, Von Noorden and Burian (1960) noticed incomplete separation between iris and trabeculum of the anterior chamber angle in patients with idiopathic scoliosis. McKusick, Weilbaecher and Gragg (1968) described a syndrome of scoliosis, short leg, cataract and nystagmus, probably caused by a recessive gene. Salleras and Ortiz de Zárate (1950) described a family which showed a sex-linked recessive inheritance of congenital ophthalmoplegia with severe myopia. One of the seven males affected also had scoliosis.

Zorab (1968) pointed out that there are four possible groups of causes for structural scoliosis. The cause may lie in the bony vertebral column and adjacent ribs, in the surrounding muscles and their nerves or blood supply, in an inequality of growth rates on the two sides of the body, or in the connective tissue.

Abnormalities in connective tissue and in general metabolism in patients with idiopathic scoliosis have been sought for some years, in an attempt to find an inborn error of metabolism. Ponseti (1968) found an excess total hexosamine content in iliac crest biopsies of patients with adolescent scoliosis. He postulated that this also occurred in cartilage cells of the vertebral plates and intervertebral discs, and that there is expansion due to hydration with excessive growth in the plates. The posterior elements do not expand and this produces a lordosis, which, as Roaf (1966) pointed out, leads to scoliosis. Ponseti also found evidence of decreased collagen which may facilitate rotation.

Rats fed with beta-aminopropionitrile have defective collagen formation and develop osteolathyris and scoliosis. A high alpha/beta chain ratio in skin samples from patients with Marfan’s syndrome and from patients with homocysteinuria suggests defective collagen formation in both syndromes. It has been suggested that homocysteine itself may limit collagen cross linkage (Harris and Sjoerdsm 1966). Scoliosis is frequent in both of these syndromes.

It is not possible to say for certain what mode of inheritance is responsible for the familial incidence in the four patients recorded here. Biochemical abnormalities have been implicated in the etiology of both scoliosis and progressive external ophthalmoplegia. It is possible that in this family the two conditions may be mediated by a common genetic biochemical disorder, although there is no proof for this attractive idea.
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SUMMARY

Four cases are presented of a syndrome of progressive external ophthalmoplegia and scoliosis occurring within one family. These patients were extensively investigated but no biochemical abnormality was detected.

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REFERENCES


