FAMILIAL CHRONIC HYPERTROPHIC POLYNEUROPATHY WITH PARALYSIS OF THE EXTREMITIES IN COLD WEATHER

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The syndrome of muscular atrophy, sensory loss and absence of tendon jerks in the extremities, associated with palpable or visible thickening of peripheral nerves, was first recognized as a clinical entity by Déjerine and Sottas[11] in 1893. They described the disease in a brother and sister, and added an earlier reported case of Gombault and Mallet[16] which had been regarded as an unusual case of tabes dorsalis. In 1906, Déjerine and Thomas[12] confirmed the pathological findings of hypertrophic interstitial neuritis in another case. Wolf[34] surveyed the literature in 1931 and managed to collect 40 cases up to that time. Several more have since been added.[21] The familial nature of the disease was emphasized by Brasch[8] in 1904 and a number of affected families have since been reported.[22,17,35,32,15,30] Other cases have occurred sporadically.

The disease may manifest itself at any time of life, varying from childhood to middle age. The sexes are equally affected. The disease is non-inflammatory and the term chronic hypertrophic polyneuropathy is used in preference to that of chronic hypertrophic interstitial neuritis, progressive hypertrophic neuritis, or maladie de Déjerine-Sottas.

The condition is insidious in onset though a long history of cold extremities is usually available. With gradual destruction of both motor and sensory components of the peripheral nerve, weakness and sensory loss in the extremities progresses. The degree of sensory and motor impairment, however, need not be equal, some cases having an almost entirely motor manifestation. Trophic ulceration is uncommon and cranial nerves are rarely affected. Root pains may be troublesome. The hypertrophy of the nerves bears no relationship to the degree of motor or sensory involvement. Recurrences and remissions of symptoms have been reported.[29,25,18]

The nerves are the seat of cellular proliferation and connective tissue is laid down in a lamellar fashion around single nerve fibres, giving an 'onion skin' appearance. The collagen tissue is derived from the Schwann cells and is quite distinct from the endoneurium.[22] However, both Schwann sheath and endoneurium may be affected. The process involves the nerve tissue from the roots to the periphery in varying degrees. Spinal ganglia may show involvement, with atrophy and fibrous overgrowth. Myelin fragmentation and the presence of 'plasmic swellings' have been demontrated.[15] Some cases may show involvement of the posterior columns, with degeneration and sclerosis.

The condition is slowly progressive and varies enormously from case to case.

The following family is placed on record not only because of the rarity of the disorder but also to describe the severe autonomic disturbance occurring with minor fluctuations in environmental temperature, resulting directly or indirectly in gross deterioration in sensory perception and flaccid paralysis of the extremities, both reversible on rewarming.

CASE REPORT

Mr. C.B., aged 28 and the father of 3 children, suffered from pain on walking, and at rest when cold. The pain had been present for the past year in the right foot, where a discharging perforating ulcer had developed during the past 6 months. At the age of 16 he noticed calluses forming under the metatarsal heads of both feet. The feet had become deformed since the age of 9 years, the deformity being that of pes cavus. For the past 3 years the patient had noticed a weakness of extremities during the winter months, particularly marked on very cold days. At times he was quite unable to walk or use his hands. The weakness was accompanied by a numbness of the feet. There has been a gradual loss

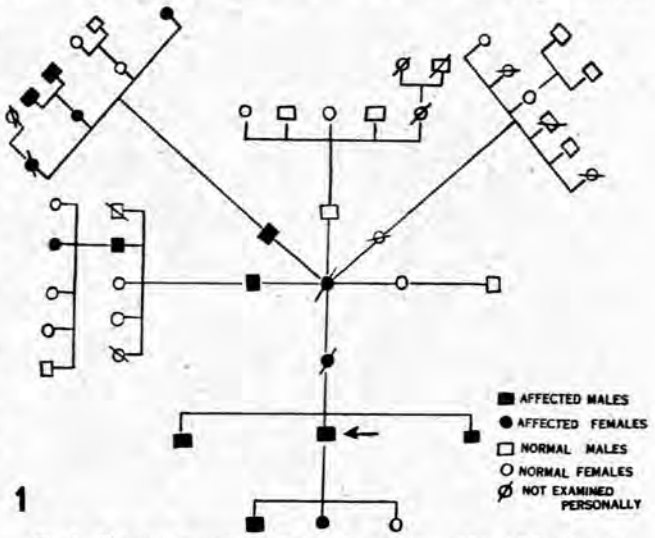

Fig. 1. Showing transmission through several generations of the disorder, with muscular atrophy, pes cavus and thickened nerves.

of weight from 212 lb. to 160 lb. over the past 3 years. He perspired profusely and had complained of cold extremities for years. He did not think there was anything wrong with other members of the family but on direct questioning he recalled that his mother, 2 uncles and a cousin had pes cavus. The family was investigated and numerous members were found to be involved (Fig. 1).

Examination

Blood pressure 140/100 mm. Hg. Cranial nerves intact, fundi normal. Marked atrophy of the small muscles of the hands and feet and, to a lesser extent, of the arms and legs. Perforating ulcer over head of 5th right metatarsal. The reflexes were present and equal coordination was normal, and in the warmth of the ward (70°F) muscle power and sensation were normal. There was palpable thickening of the peripheral nerves. The cervical cutaneous nerves stood out like cords as the head was turned putting them on stretch.

Haemoglobin, 15 g./100 ml. Leucocyte count, 4,900/c.mm. Differential count, normal. Blood urea, 15 mg./100 ml. Serum G-O transaminase, 51 units/100 ml. Serum glutamic-pyruvic transaminase, 75 units/100 ml. Serum sodium, 132 mEq./litre. Serum magnesium, 1·8 mEq./litre. Serum creatinine, 0·8 mg./100 ml. Wasserman reaction negative. Random blood sugar, 108 mg./100 ml. Serum calcium, 4·7 mEq./litre. Plasma inorganic phosphorus, 3·8 mg./100 ml. Total serum protein, 8·3 g./100 ml.; albumin, 3·04 g./100 ml.; alpha-1 globulin, 0·76 g./100 ml.; alpha-2 globulin, 1·10 g./100 ml.; beta globulin, 1·68 g./100 ml.; gamma globulin, 1·72 g./100 ml. Serum protein-bound iodine, 4·0 μg./100 ml. Erythrocyte sedimentation rate, 24 mm. in first hour.

The cultivation of the pus from the ulcer showed infection with *Staphylococcus aureus* sensitive to chloromycetin and erythromycin.

The average 24-hour urinary volume was 2,500 ml., containing sodium 57 mEq./litre, potassium 11 mEq./litre, phosphorus 650 mg., and creatinine 1,300 mg., of which 50 mg. was creatine.

ECG normal. X-rays of chest and skull normal.

X-rays of the right foot showed marked destruction and sclerosis of the 5th metatarsal bone.

The posterior auricular nerve was biopsied and revealed the following change: (1) Thickening of the perineurium, (2) definite collagenous thickening around many of the individual nerve fibres, (3) thinning of the myelin sheaths, and (4) in longitudinal sections a separation of the nerve fibres with occasional strands of collagen between these structures.

On muscle biopsy a few abnormal small fibres were seen, with an increased number of dark small nuclei.

Skin biopsy showed evidence of swelling of the endothelial cells of some of the small blood vessels. At one level a definite acute vasculitis was evident in some small vessels in the deep part of the dermis.

Electromyographs showed normal motor unit activity in the proximal muscles. The small muscles of the hand produced a mixed pattern on maximum contracting, indicating a 40% reduction in contracting muscle fibres.

When the patient was re-examined after walking about the hospital garden on a cold winter morning of 45°F, marked weakness of the legs and complete loss of sensation to all modalities was found, involving the right foot and leg and the left foot. This rapidly disappeared when he re-entered the warm hospital wards. The patient was constantly perspiring, most noticeably in the hands and feet.

Skin temperatures were recorded at various sites before and after reflex lumbar heating and after the administration of 25 mg. of priscol by mouth. The results are shown in the following table (in °F):

Skin Tested	*Resting*	*½ hour after lumbar heating*	*½ hour after oral priscol*
Dorsum of right arm ..	85·0	85·6	89·0
Dorsum of right hand ..	75·2	80·0	82·5
Ventral surface of left arm	86·2	86·4	88·3
Left palm	75·6	88·0	88·0
Front of right leg ..	83·5	81·6	88·0
Dorsum of right foot ..	84·6	87·0	93·8
Back of left leg	80·0	80·0	90·2
Sole of left foot	76·8	78·4	89·0
Dorsum of left foot ..	76·8	80·2	90·0

Electromyographic studies on the small muscles of the hand were repeated during cooling of the limb; the results are seen in the tracings in Fig. 2, which show the falling out of motor unit activity and the decreasing potentials. At 68°F there was no recordable activity on attempted contraction of the muscles. During this stage there was no response of the muscle to direct electrical stimulation. There were also no changes in the electrolytic content of the blood. Kymographic studies were also carried out at various temperatures in a water bath, the results of which are shown by the tracings in Fig. 3, which demonstrate the weakness occurring in the muscle of the forearm at lower temperatures. The arm was submerged in a water bath, and a 5 lb. weight attached to the fingers was elevated as the hand was closed; the excursions of the weight were recorded on a rotating drum.

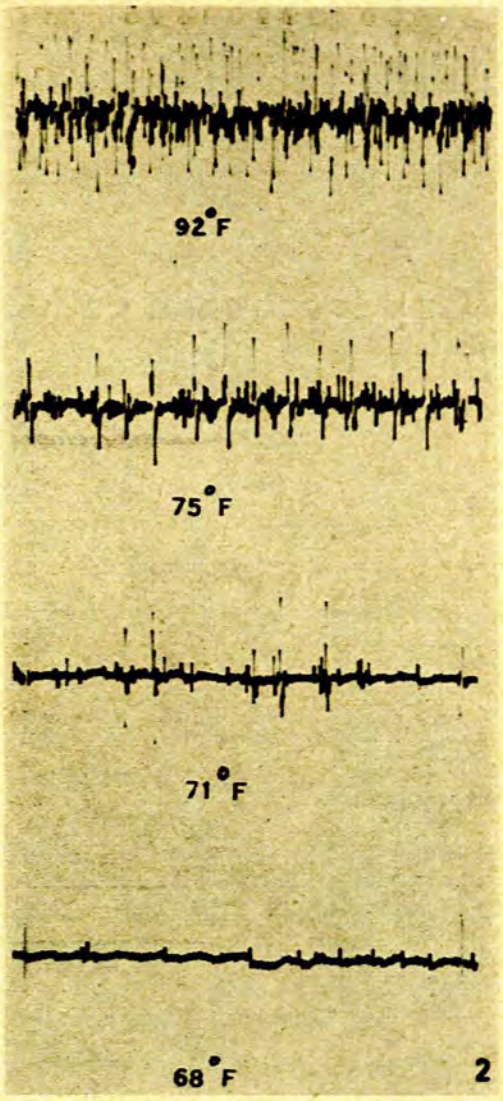

Fig. 2. First dorsal interosseous, maximum contractions at various temperatures. Voltage 100 μv./mm. Paper speed 20 msec./mm.

DISCUSSION

There are several reports of cases where hypertrophic neuritis has been associated with other features, e.g. kyphoscoliosis, intention tremor, dysarthria, fasciculation of muscle, and sensory ataxia. It is not surprising that some cases of this disease have been misdiagnosed as tabes dorsalis, like Gombault and Mallet's original case in 1889.[16] Others have been confused with Friedreich's ataxia or peroneal muscular atrophy.

Refsum[27,28] described a syndrome occurring in both adults and children, which he called 'heredopathia atactica polyneuritiformis', and Ashenhurst *et al.*[1] have recently reported a further 3 cases occurring in one family. This syndrome is characterized by atypical retinitis pigmentosa, chronic progressive polyneuritis, high protein in the CSF, with cyto-albuminological dissociation, signs of cerebellar dysfunction, occasional nerve deafness, abnormal pupillary reactions, and anosmia. Skin changes may also occur in the form of ichthyosis, as well as ECG conduction abnormalities. Changes characteristic of hypertrophic interstitial neuritis have been reported in the peripheral nerves in one case.[31]

It is possible that several of the cases of hypertrophic polyneuritis in the literature showing kyphoscoliosis,[16,22,7] or kyphoscoliosis with nystagmus[11] or with intention tremor,[36,10] are examples of a mild form of Refsum's syndrome. It may, in fact, be argued that Refsum's syndrome on the one hand, and progressive hypertrophic neuropathy on the other, represent two extremes or near-extremes of a particular spectrum of disorder.

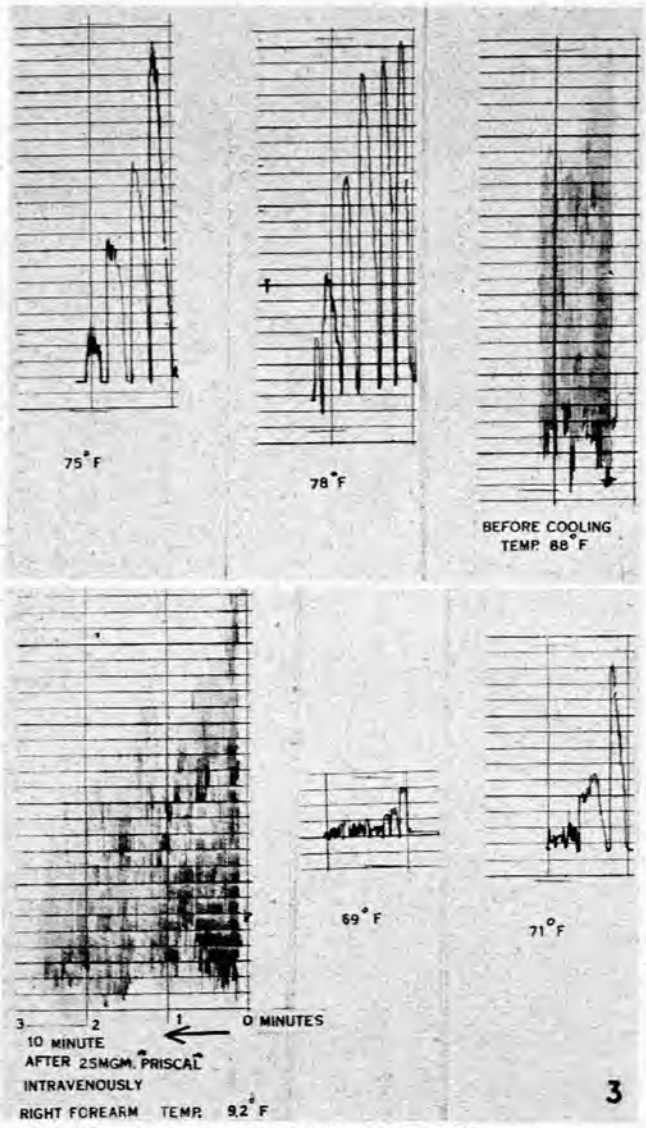

Fig. 3. Drum rotating from right to left recording repetitive grasping movements of the right hand elevating a 5 lb. weight.

As stated earlier, trophic disturbance is rare in hypertrophic polyneuropathy, whereas it is not an uncommon feature of certain other disorders, some of which may be familial.

In 1913 Price[26] described a disease affecting the spinal cord with the production of central cavities. This was later regarded as a form of gliosis, often associated with a peripheral neuritis and having a familial tendency. It is probably identical with a condition described by Morvan[23] 30 years earlier as affecting the fishermen of Brittany.

Syringomyelia has long been recognized as a cause of trophic ulceration. This condition, and also neurofibromatosis and tuberous sclerosis have been considered to be a spongioblastosis with resultant incomplete developmental closure of the spinal cord.[3,9] All three of these conditions may occur in families.

The condition of familial perforating ulcer of the foot was considered by Hicks[19] to be a separate clinical entity. Besides the trophic ulceration of the feet there was often an associated deafness which is of particular interest because of this occurrence of deafness in the Refsum syndrome. Thevenard[33] also recorded familial perforating ulcer of the foot as a condition distinct from lumbodorsal syringomyelia. Despite these opinions, however, typical familial cases of perforating ulcer have been observed[24,4] and later found to be associated with typical or atypical syringomyelia.

Trophic ulceration may complicate many diseases of the peripheral sensory nervous system; it may be associated with leprosy, syphilis, traumatic lesions, primary amyloidosis, and occasionally peroneal muscular atrophy.[14] Several authors have commented upon the occurrence of associated vascular disease in polyneuropathy.[20] Van Bogaert[6] has considered vascular lesions in some cases to be secondary to a disorder of the peripheral nervous system, and that a vicious circle is thus established.

Denny-Brown,[13] in his anatomical study of members of a family with perforating ulcers of the feet, emphasized the degeneration of the spinal ganglia and accumulation in them of a hyaline substance, and an associated secondary amyloid degeneration of the blood vessels. Their case also showed degeneration of the posterior columns, posterior roots and peripheral nerves. Van Bogaert[5] described further cases of 'hereditary polyganglionic radicular disease', affecting both nerves and vascular tissue, which showed deposition of a hyaline substance that was distinct from amyloid. He found rarefaction of the axis cylinders and fibrosis of the perineurium, with subintimal proliferation of the small arterioles.

There is another group of disorders which may give rise to trophic disturbances. This group includes the case with dysfunctions presumably of the sympathetic nervous system, e.g. Raynaud's disease and acrodynia. In these cases, besides the hypo- or hyperaesthesia, there is often hyperhidrosis, coldness, swelling and pain in the affected extremity.

CONCLUSION

The family presented in this paper shows no evidence of retinitis pigmentosa, kyphoscoliosis, pathology of the dorsal column, intention tremor, deafness, or elevation of the protein in the CSF; they are considered to be typical cases of hypertrophic polyneuropathy associated with a severe peripheral sympathetic nervous overactivity, resulting in vascular changes which establish a vicious circle as regards the trophic integrity of the extremities.

The sensory changes in this case have been largely prevented by the continuous administration of priscol in doses of 50 mg. *t.d.s.* This regime has seen the patient through the winter months and now with the warmer weather he has been able to do without the vasodilator. With the aid of antibiotics the ulcer has almost healed.

SUMMARY

A case of hypertrophic polyneuropathy presenting with a perforating ulcer of the foot and a periodic flaccid paralysis of the extremities during cold weather is presented. Other members of the family were examined and several members of live generations were found to be affected.

Other familial conditions with either hypertrophic polyneuropathy or perforating ulcers of the feet are discussed.

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