Thyrotoxic neuropathy (Basedow's paraplegia)

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SYNOPSIS Polyneuropathy is a rare but possible manifestation of severe hyperthyroidism. The patient reported here developed a polyneuropathy affecting mostly leg muscles (Basedow's paraplegia) during the course of severe thyrotoxicosis. The polyneuropathy was confirmed with sequential electrophysiological studies of nerves and muscles and by muscle biopsy. The involvement of the proximal leg muscles is also interpreted as a neuropathic or nerve-mediated process rather than a concomitant thyrotoxic myopathy.

Several muscle diseases have been associated with hyperthyroidism. They include acute and chronic thyrotoxic myopathies, exophthalmic ophthalmoplegia, periodic paralysis, and myasthenia gravis (Ramsey, 1968, 1974). In contrast to muscle, peripheral nerve involvement in hyperthyroidism has received little attention. We have recently studied a severely thyrotoxic patient and have demonstrated the presence of a peripheral neuropathy virtually restricted to the lower extremities. A number of similar cases of flaccid leg weakness associated with thyrotoxicosis were described in the European literature of the late nineteenth century, as reviewed by Sattler in 1908 (Sattler, 1952). The clinical condition was called 'Basedow's paraplegia' (Charcot, 1889; Joffroy, 1894).

CASE REPORT

The patient, an 18 year old black male with familial hyperthyroidism, was admitted to the University of Virginia Hospital with a four week history of severe leg weakness and dysaesthesias. He had suffered from a toxic goitre for three months. On examination, he had pronounced exophthalmos with lid lag, a warm grossly enlarged thyroid gland, dysphonia, and marked signs of adrenergic overstimulation including tachycardia, diaphoresis, agitation, and a rapid tremor of the outstretched fingers.

The neurological dysfunction was limited to the motor and sensory systems except for weakness of the superior rectus muscle of the left eye. Marked proximal and distal leg weakness was associated with moderate muscular atrophy, severe hypotonia, and absent tendon reflexes in the legs only. With the exception of slight weakness of the intrinsic hand muscles, the musculature of the rest of the body was strikingly normal. This marked selectivity of leg weakness resembled that of patients with flaccid paraparesis. The patient walked with great difficulty, showing marked steppage and waddling gait. When he rose from a sitting position, his paraplegia-like weakness became more apparent as shown in the movie frames of Fig. 1. All proximal and distal leg muscles were equally affected with slightly more than anti-gravity strength in the right leg and less than anti-gravity strength in the left. Partial sensory loss, limited to the left leg, included decreased pain and light touch perception up to the groin and impaired proprioception in the foot and toes. There was no evidence of cerebellar, corticospinal tract, or sphincter dysfunction.

Laboratory data confirmed hyperthyroidism: T4 (Murphy-Pattee) estimation was 28 units (normal=5.2–14 units), T3 resin uptake was 53 units (normal=24–35 units); plasma cholesterol level was 2.59 mmol/l. An electrocardiogram showed sinus tachycardia. The remainder of the laboratory tests, including serum calcium, sodium, potassium, CO₂ and chloride were normal except for leucopenia (WBC 4000/mm³ with 34% polymorphonuclear cells).

Two days after admission, the patient was

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FIG. 1. *Selected frames from movie picture showing the patient rising from a sitting position. A strong arm and trunk musculature is used to lift the body above the weak legs. Notice the passive position of the feet during this effort.*

treated with propranolol (320 mg/day) and propylthiouracil (1200 mg/day) for two weeks. This treatment did not control the thyrotoxicosis and was discontinued because of marked leucopenia and high fever. Repeated blood cultures were consistently negative. Iodine therapy (Lugol's solution) promptly reversed his deteriorating clinical condition and was followed by a subtotal thyroidectomy. The day after surgery, the patient again developed high fever with sterile blood cultures. He was treated with Lugol's solution only, became afebrile in two days and was discharged without medications in euthyroid state. The two febrile episodes were interpreted as 'thyroid storms'.

Sequential electrophysiological testing (described below) confirmed the clinical impression of a severe peripheral neuropathy with progressive slowing of motor and sensory nerve conductions in the lower extremities and electrical

signs of denervation in distal, but not in proximal, leg muscles. Electrophysiological evidence of myasthenia gravis or other disorder involving the neuromuscular junction was not found. A biopsy specimen from the quadriceps muscle done at the time of the thyroidectomy showed severe muscle fibre atrophy indistinguishable from that of denervation.

One month after thyroidectomy (6 May 1974), the patient showed significant recovery of strength in proximal leg muscles without improvement in distal muscles. Walking was performed with less difficulty but hip waddling and steppage were still present. Ten weeks after surgery (17 June 1974), the extraocular muscles were found to be completely normal and the muscle strength in the legs continued to improve; the patient now could bend without falling. Fasciculations were seen in the quadriceps and the deep tendon reflexes were now obtainable at the knee and even at the ankle

using reinforcement. Sensory deficit also improved, vibratory sensation became normal, and the hypaesthesia changed to a stocking type of minimal degree. Five months after surgery (20 September 1974), the sensory deficit had disappeared. The patient's strength continued to improve, more in the proximal than in the distal muscles. The hip waddling and steppage were less pronounced. At seven months (30 November 1974), the patient could walk without much difficulty, although he still had bilateral foot-drop and could barely stand on his toes. Recovery was still incomplete one year after the onset of leg weakness.

ELECTROPHYSIOLOGICAL STUDIES The initial studies were performed on 14 March 1974, nine days after the onset of treatment with propranolol and propylthiouracil. Needle electromyography of the right and left quadriceps muscles revealed an interference to mixed pattern of decreased amplitude (less than 2.0 mV) with maximum effort. Activity at rest was not seen. The majority of the motor unit potentials were irregular, of low amplitude and short duration. Approximately 20% of the motor unit potentials were short and polyphasic. The left quadriceps was more severely affected than the right. The same findings were also seen in the right tibialis anterior muscle, but the clinically strong left biceps femoris was completely normal. The impression was that of 'electromyographic myopathy'.

Evoked potential study of the left abductor digiti minimi muscle with stimulation of the ulnar nerve revealed a normal amplitude of the evoked potential (8 mV) and no spontaneous decrement when stimulated at a rate of 3/s. Minimal post-tetanic facilitation and no post-tetanic exhaustion or decrement at 3/s stimulation were observed in the four minutes after maximal voluntary contraction.

Motor and sensory conduction velocity studies revealed abnormalities in the left peroneal and left sural nerves but not in other nerves of the legs (Table). Motor and sensory conduction velocities in ulnar and median nerves were within normal limits.

The above studies were repeated on 8 April 1974, two weeks after the first 'thyroid storm' and one week after surgery. They showed improvement of the 'myopathic' electromyogram from the right and left quadriceps muscles with almost complete disappearance of the short polyphasic and other 'myopathic' type motor unit potentials. Denervation potentials were never seen in these proximal muscles. By contrast, the electromyogram from both right and left tibialis anterior muscles, also of myopathic type in the initial study, now revealed frank denervation with fibrillation and positive sharp waves in more than two-thirds of muscle insertion sites. This was accompanied by severe loss of motor units with few remaining motor unit action potentials. The motor conduction velocities in all distal nerves of the legs were now severely affected (Table).

Subsequent nerve conduction studies at three and five months (6 May and 17 July 1974) after thyroidectomy demonstrated further deterioration in the motor and sensory conduction velocities in the lower extremities and for the first time minimal slowing of the sensory, but not the motor, conduction velocities in the upper extremities.

MUSCLE HISTOCHEMISTRY The left quadriceps muscle was biopsied at the time of thyroidectomy (2 April 1974) two weeks after the first and six days before the second electromyographic studies. The muscle specimen was frozen for histochemical incubation and histological staining for haematoxylin and eosin, modified Gomori's trichrome, DPNH dehydrogenase, SDH, phosphorylase,

TABLE
SEQUENTIAL STUDIES OF NERVE CONDUCTION

	Peroneal				Tibial				Sural	
	R	L	R	L	R	L	R	L	L	L
14 March	40.6	34.7	5.6	7.6		44.7		4.5	40.6	3.7
8 April	30.2	25.6	6.9	8.9	36.2	31.6	8.2	6.8		
6 May	28.6	nEP	11	nEP	32.6	34.1	7.1	7.5	35.0	5.1
17 July	25.2		8.7	nEP	31.5	nEP	6.3	nEP	nEP	nEP
	MCV		DML		MCV		DML		SCV	
Normal range	42-58 m/s		7.8 ms		40-52 m/s		8.5 ms		42-56 m/s	
									DSL	
									4 ms	

Motor and sensory conduction velocities (MCV and SCV) in metres per second (m/s) and distal motor and sensory latencies (DML and DSL) in milliseconds (ms). No evoked potential to maximal nerve stimulation is abbreviated as nEP.

PAS, esterase, alkaline phosphatase, and myofibrillar ATPase (pH 4.4, 4.7, and 10.2).

The muscle sections revealed pronounced and extensive atrophy of muscle fibres (Fig. 2). The atrophic angular fibres were scattered almost regularly throughout the specimen in groups of variable size, interspersed with normal muscle fibres. The DPNH staining was abnormally increased in some but not all the small fibres (Fig. 3). With myofibrillar ATPase, the groups of atrophic fibres were composed of mixtures of

three histochemical fibre types (Figs 4, 5). Likewise, the intact fibres were also a mixture of three types without predominance of any type. The non-selectivity for the atrophic, as well as for the normal fibres was also demonstrated with the method for DPNH dehydrogenase, phosphorylase, SDH, and esterase. Target fibres and type grouping were not seen. There was one small blood vessel with a perivascular cell reaction near two necrotic muscle fibres. No other abnormalities including abnormal material were seen in vessels or

FIG. 2. Atrophic muscle fibres are scattered through the field in small and large groups. Modified Gomori's trichrome, $\times 120$.

FIG. 3. Some of the atrophic muscle fibres show dark, increased staining in the DPNH reaction $\times 120$.

FIG. 4. The groups of atrophic fibres contain type I (light) and type II (dark) fibres. Myofibrillar ATPase reaction at pH 10, $\times 120$.

FIG. 5. The groups of atrophic fibres also contain type IIB fibres with intermediate staining. Myofibrillar ATPase reaction with preincubation at pH 4, $\times 120$.

muscle fibres. Nerve bundles were not present in the specimen. These morphological abnormalities in the left quadriceps muscle were thought to be similar to those of acute denervation, although the electromyogram of the same muscle did not show electrophysiological evidence of such denervation.

DISCUSSION

The patient described here presented with clinical evidence of polyneuropathy after three months of symptomatic hyperthyroidism and four weeks before treatment started. The clinical evidence for polyneuropathy consisted of marked distal, in addition to proximal, muscle weakness, muscle atrophy, almost absent tendon reflexes, and sensory deficit as described above. The legs were so predominantly involved that the clinical picture strongly resembled that of flaccid paraparesis.

The first electrophysiological evidence of nerve involvement was obtained in the initial studies nine days after admission and medical treatment. Frank electrical denervation of distal leg muscles and marked slowing in conduction of peroneal, tibial and sural nerves were demonstrated 20 days later, two weeks after the first 'thyroid storm'. The time course of these electrophysiological abnormalities indicated the presence of an initial polyneuropathy and a subsequent acute exacerbation coincident with the worsening of the thyrotoxicosis.

Follow-up clinical and electrophysiological observations after subtotal thyroidectomy and cure of thyrotoxicosis showed further slowing of nerve conduction in the legs and new abnormalities in the arms, despite definite improvement in muscle strength and sensory deficit. This lack of correlation between nerve conduction velocities and clinical recovery has also been observed in the Guillain-Barré syndrome (Bannister and Sears, 1962; Pleasure *et al.*, 1968) and probably represents changes in myelin thickness during remyelination.

Histochemical studies in a biopsy specimen from a proximal leg muscle showed severe muscle fibre atrophy which, like denervation, was grouped or scattered throughout the specimen and involved all histochemical fibre types. The absence of electrical denervation in this proximal muscle, although suggesting that the muscle involvement was not classical denervation, does not exclude other nerve-mediated mechanism, or early stages of denervation. Furthermore, the presence of fully developed electromyographic denervation in the distal leg muscles of our

patient indicates that the same neuropathic process might have affected his proximal musculature. The alternative of an independent proximal myopathy was not supported by our histochemical or electromyographic studies except for a 'myopathic EMG'. In our view, a 'myopathic EMG' does not necessarily mean primary muscle disease since it has been frequently associated with several types of muscle fibre atrophy of undetermined nature (Warmolts and Engel, 1970).

Since the initial electrophysiological evidence of frank denervation occurred several weeks after treatment began, the possibility that propylthiouracil may have aggravated an already existing polyneuropathy cannot be ignored. However, neurological disorders complicating therapy with propylthiouracil are rare. Vertigo, paraesthesias, and dysaesthesias have been reported (Vanderlaan and Storrie, 1955; Crile and McCullagh, 1951). To our knowledge, objective neuropathy has not been described after its use.

Propylthiouracil, a thionamide, inhibits the incorporation of iodide into the precursors of the thyroid hormones (Solomon, 1973). The precise mode of action of this drug is unknown (Burgi and Labhart, 1974), but no direct neurotoxic effect has been described. However, adverse side-effects, including agranulocytosis, are well known (McGavack and Chevalley, 1954). In our patient, bone-marrow toxicity causing leucopenia followed high-dose therapy with propylthiouracil; hence, the drug, acting in concert with the worsening of thyrotoxicosis and subsequent 'thyroid storm', may have had a similar adverse effect on neural tissue.

In summary, we believe that our patient had a covert sensorimotor polyneuropathy as a presenting manifestation of his hyperthyroidism. The continued worsening to a 'thyroid storm' and perhaps the treatment with propylthiouracil resulted in an overt acute polyneuropathy. This polyneuropathy involved both proximal and distal leg muscles with different severity. A concomitant thyrotoxic proximal myopathy could not be separated from the muscle involvement by the polyneuropathy.

THYROTOXIC NEUROPATHY IN LITERATURE Paraplegia-like weakness during severe hyperthyroidism was first described by Charcot in one of his *Leçons du Mardi* (1888). In the paper, 'Nouveaux signes de la maladie de Basedow' (1889) he described the clinical findings as follows:

'Cette paraplégie est flasque, sans aucun phénomène spasmodique; elle ne s'accompagne pas de

douleurs fulgurantes, les réflexes sont absents. Il n'y a aucun trouble de la sensibilité, il n'y a pas de participation de la vessie. Elle ne peut se confondre avec la paraplégie hystérique. Il semble donc qu'il y ait un type particulier de paraplégie dans la maladie de Basedow, dont le premier phénomène serait l'effondrement des jambes, qui n'en est qu'une forme atténuée'.

This flaccid paraplegia with absent reflexes, without sphincter disturbances but occasionally with some sensory deficit, was reported at least 13 times by early European authors (Sattler, 1908). The condition was called 'Basedow's paraplegia' by Joffroy (1894). After these early reports, the term 'Basedow's paraplegia', to our knowledge, has been mentioned only twice in journal titles since 1940 (Sanghvi *et al.*, 1959; Fridberg and Egart, 1970) and also by Tyler and Adams in *Harrison's Principles of Internal Medicine* (1974). We believe our patient to be another example of this rare condition.

Neural involvement in severe thyrotoxicosis is supported by Jan Waldenström's review of acute thyrotoxic myopathy (Waldenström, 1945), a condition described by Russell Brain (Brain and Turnbull, 1938) that Waldenström preferred to call 'acute thyrotoxic encephalo- or myopathy'. Waldenström described it as

'usually associated with signs of thyrotoxic crisis or thyrotoxic coma and the most striking symptoms are those of bulbar palsy. Muscular weakness of the limbs and loss of reflexes also occur. Severe cerebral symptoms, such as paraphasia, acalculia and psychosis with hallucinations seem to indicate that the disorder is often either accompanied (or caused?) by a real encephalopathy. It may be very difficult to determine if the causes are of cerebral or muscular origin'.

This condition was distinguished from that of myasthenia gravis associated with thyrotoxicosis (Millikan and Haines, 1953).

More recently, Ludin *et al.* (1969) revived interest in neuropathic involvement in hyperthyroidism by reporting eight patients with a 'neurogenic' electromyogram in distal leg muscles. They postulated that their patients had a subclinical polyneuropathy. Later, Chollet *et al.* (1971) mentioned two cases of thyrotoxic goitre and polyneuropathy with definite slowing of nerve conduction. Previously reported electrophysiological studies in thyrotoxic myopathy (Harvard *et al.*, 1963; Ramsey, 1965) were not sufficiently

complete to rule out the presence of peripheral nerve involvement. Studies of multiple nerves and sequential determinations, as done in our patient, are often necessary to demonstrate a conduction defect in peripheral nerves.

In conclusion, peripheral nerve involvement in hyperthyroidism is a rarely reported, but possible, manifestation of severe thyrotoxicosis. In these situations the commonly reported muscle weakness may change to a frank polyneuropathy. It is also possible that what we call thyrotoxic myopathy is actually a neuropathic or nerve-mediated process not fully expressed as classical denervation. The effect of thyroid hormones on peripheral nerve function appears to be a pertinent subject of appropriate investigation.

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