A Neuropathic Syndrome of Uncertain origin

Review of 100 cases

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A neuropathic syndrome with features which do not conform to any recognised disease pattern has been known to occur in the West Indies for some years. It was first recorded by Strachan in 1888, and there have been other brief accounts since. The most detailed comes from Scott (1918) who called the condition a "Central Neuritis". A similar syndrome has been reported from North and West Africa, Trinidad, Malaya, India, Java, Hong Kong and Spain during the Spanish Civil War (Spillane and Scott, 1945; Stannus, 1911; Moore, 1946; Money and Scott-Smith, 1955; Metevier, 1947; Pallister, 1940; Nichols, 1935; Hobbs and Forbes, 1946; and Crawford and Reid, 1947; Peraita, 1942). Dietary deficiency or imbalance is regarded as the main causative factor.

The clinical features of 100 cases investigated at the University College Hospital of the West Indies since 1953 are to be presented and the aetiology discussed. It has not been possible to assess the incidence of the disease in the island but all the cases came through routine hospital channels and no attempt has been made to collect them from other hospitals or clinics. Most cases came from widely scattered country areas and there was no evidence of concentration in any given part.

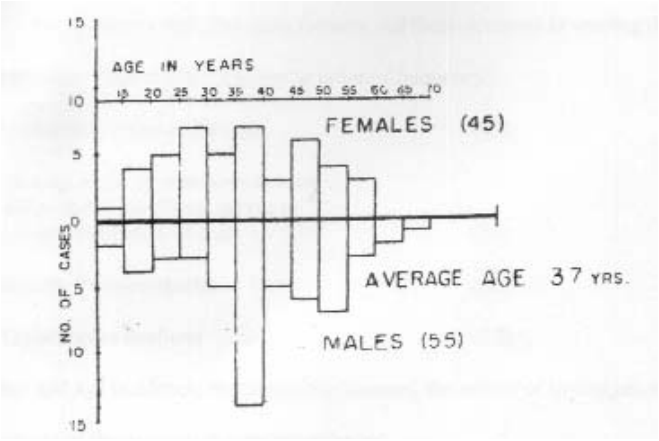

Fig. 1. Age and sex incidence.

The syndrome had four main features and these occurred in varying degrees and combinations. They are listed below in order of frequency:

(a) Upper motor neuron damage (93)
(b) Damage to the first sensory neuron either in the peripheral nerves or posterior columns or both (54)
(c) Retrobulbar neuropathy (26)
(d) Eighth nerve deafness (1 2)

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The sex and age incidence, the presenting features, the results of investigations and a rough assessment of the patient's dietary are recorded.

There is an equal sex incidence and the age distribution is fairly even from 15 to 60 with some rise in the 35 – 40 group.

Table 1: Presenting Symptoms and Mode of Onset

	No of Cases
Presenting Symptoms	
Weakness in legs (often associated with cramping)	100
Sensory disturbances (numbness, paraesthesia)	26 (including 10 burning feet)
Urinary disturbances (hesitancy, precipitancy, urgency, incontinence)	61
Visual impairment	8
Deafness	12
Pain (dull lumbar ache or sharp pains in thighs and legs)	30
ONSET Gradual	89
Sudden	11

Of the symptoms, weakness in the legs was the prominent presenting feature in all cases although in a number there had been vague aches or pains in the limbs or back for some time before weakness appeared. Both limbs were usually involved but the symptom sometimes occurred earlier and was more marked in one limb than in the other. The onset was gradual in 89 progressing over a few weeks or months to maximum disability and slowly regressing thereafter in some but usually remaining stationary indefinitely although an acute severe febrile illness or, in one case, pregnancy produced deterioration. In 11, it came on suddenly. None showed the classical episodic progression and regression of disseminated sclerosis. The time from onset until they came under observation is shown in (Fig. 2). No case has yet been under observation for more than four years.

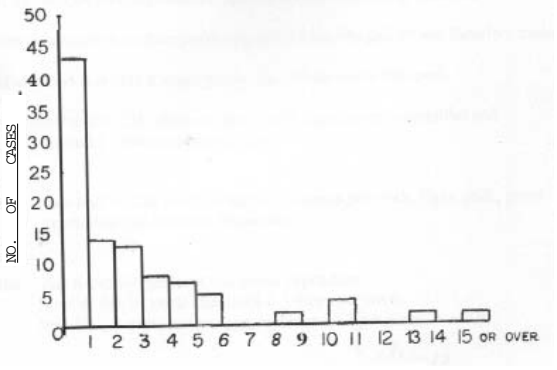

Fig. 2. Time in years from onset till coming under observation at the University College Hospital of the West Indies

Paraesthesia or numbness were complained of by only 22 patients, although sensory changes were demonstrable in 54. Twenty-seven had pain. A dull lumbar ache with or without shooting pains in the legs and feet in 19 and burning feet in 10.

Hesitancy, precipitancy, urgency or less often incontinence of urine was present in 61 patients – this usually appeared some time after the onset of weakness. Only 8 cases complained of defective vision although scotomata or constricted fields with optic atrophy were found in 26. Nerve deafness was present in 12. However, no careful assessment of hearing was done unless the patient complained of deafness and minor defects may have been overlooked.

The clinical findings in the nervous system are shown in Table 2. Few associated signs of vitamin deficiency were present.

The results of the various investigations carried out are summarised in Table 3.

The diet assessment was done purely on questioning the patient and therefore cannot be regarded as reliable and it is only a rough guide. The ratings are as follows:-

very good – meat and/or fish (fresh or salt + milk, eggs, green vegetables and legumes – daily or almost daily.

good – meat and/ or fish (fresh or salt) 3 – 4 times per week. Eggs, milk, green vegetables and legumes frequently.

fair – diet basically rice, root and green vegetables.
Meat or fish in small quantities 2–3 times per week.
Milk (½ – 1 pint) and/or eggs, legumes 1–2 times per week.

Table 2: Neurological Findings

(1)	MOTOR			
	Reflexes exaggerated and tone increased – legs only			44
		legs and arms		49
	Reflexes absent			7
	Clonus – some unilateral			55
	Plantar response – extensor – bilateral			70
		unilateral		5
	– equivocal			7
	– flexor			18
(2)	SENSORY			
	Posterior column alone			
	Vibration and position sense diminished or absent		24	33
	+ light touch diminished or absent		9	
	Posterior column + peripheral nerve damage			
	Vibration and position sense + pain diminished or absent		6	
	" " " " + light touch diminished or absent		8	21
	Pain alone diminished		5	
	Pain and light touch		2	
2				
	Associated with lateral column damage		47	54
	Without lateral column damage		7	
(3)	OPTIC NERVE			
	Marked temporal pallor – uni or bilateral with diminished visual acuity			29
	Field defects – scotomata central or paracentral		23	
	– constricted		3	26
(4)	VIIIth NERVE DEAFNESS			12
	5 had absent deep reflexes with posterior column lesion only			

poor – diet mainly rice, bread, root and green vegetables: Meat and/or fish 1– 2 times per week probably in small quantities. Legumes sporadically. Milk or eggs occasionally.

very poor – diet rice, bread, root and green vegetables
Meat or fish or legumes rarely more than once per week. Milk or eggs very rarely.

The results are shown in Table IV

Table 3: Investigations

(1)	X-RAY CERVICAL SPINE			
	Not done			16
	Normal			64
	Abnormalities		Av. age	
	Narrow disc space(s)	7	42	
	O.A. changes	5 (3 mild 2 mod. severe)	45	
	Narrowing + OA	8 (4 " 4 " ")	45	20
(2)	V.D.R.L. (blood) positive			30 (only 3 over dil.of 1:4)
(3)	FRACTIONAL TEST MEAL			
	Not done			10
	Free acid present			45
	Free acid present after histamine			20
	Histamine fast achlorhydria			25
	Average age		49	
	Sex – male		15	
	– female		10	
	Diet – not noted		6	
	– very poor		5	
	– poor		7	
	– fair		4	
	– good		3	
	Lesion lateral, column only		13	
	Lesion lat. col. + post. col.		12	
	Optic atrophy		4	
	VIII nerve lesion		2	
(4)	C.S.F. FINDINGS		6 (+ 1 spoilt)	
	Not done			
	Protein 0 – 30 mg. %		30	
	30 – 60 mg. %		46	
	60 – 100 mg. %		11	
	100 + mg. %		5 (max. 150)	
	Paretic curve		20	
	V.D.R.L. all negative (positive cases excluded from series)			
(5)	LIVER FUNCTION TESTS			
	Not done		30	
	Normal		20	
	Abnormal (most with reversal of A/G ratio)		50	
(6)	LIVER BIOPSIES – 19 done			
	Slight fibrosis (normal L.F.T.)	1		
	Some cellularity (grossly abnormal L.F.T.)	1		
	Negative	17		

TABLE 4: Diet.

Very good	7
Good	17
Fair	18
Poor	25
very poor	20
No record	13

DISCUSSION

The syndrome is one in which the main brunt of the damage is borne by the pyramidal tracts. The posterior columns are also affected in about half the cases although on clinical grounds alone it is not possible to determine whether, when the first sensory neuron for proprioception is damaged, the lesion lies in the peripheral axon or in the central process which makes up the posterior column. It is assumed however, that the lesion is confined to these latter when there is little interference with pain and temperature sensation and the motor elements of the peripheral nerve appear intact.

Pain sensation and discriminative touch can be affected but much less frequently and to a lesser degree. It is probable that when appreciation of light touch is defective peripherally, it is a further indication of damage either in the peripheral nerve or posterior column where these fibres also travel.

The visual impairment in 26 of the cases is almost certainly due to retrobulbar damage to the optic nerve, the macular bundle being mainly involved. It is to be remembered that the retrobulbar fibres have no neurolemmal sheath and accordingly are structurally as vulnerable as the posterior column and lateral tract fibres. From a strictly anatomical point of view however, they are the analogue of the second sensory neuron. As regards the 8th nerve lesion, it is probably located in the central processes of the first sensory neurons between the spiral ganglion of the cochlea and the dorsal and ventral cochlear nuclei in the medulla. It is interesting to note that this portion of the nerve is destitute of a neurolemnal sheath (Skinner, 1929). In 7 cases only was the clinical picture one of a peripheral neuropathy with the damage confined to the sensory paths including the afferent portion of the spinal reflex.

Marked wasting and loss of power in the muscles concerned did not occur. Thus these cases closely resembled tabes dorsalis but there were no pupillary changes or other features of this condition. There was an associated nerve deafness or retrobulbar neuropathy or both in most of these patients. The blood and C.S.F. serological tests for syphilis were negative. It could be argued that in spite of all these points syphilis was primarily responsible but it is unlikely.

Information about the pathological aspects of this condition is very scanty. Only one patient in this series has died so far and unfortunately an autopsy was not obtained. Scott (1918) described an out-break of an acute or sub-acute neurological disorder in sugar workers in Jamaica. The presenting features were numbness, tingling and burning in the feet, dimness of vision, ataxia, absence of reflexes and deafness associated with persistent diarrhoea. In two fatal cases, the pathological findings in the nervous system were degeneration in the posterior columns without evidence of any inflammatory damage. There was also degeneration in the spinocerebellar tracts but the lateral corticospinal paths were only minimally involved. There was also severe damage in the posterior spinal roots and posterior root ganglia. Scott's cases much more closely resemble the 6 cases of this series referred to in the last paragraph than the majority where the lesion is, from a clinical stand point, dominantly in the lateral corticospinal tracts and there is no evidence of cerebellar tract involvement. Such ataxia as occurred could be explained on impaired position sense and/or weakness from upper motor neuron damage. Recently Fisher (1955) has given an excellent and detailed account of the postmortem neurological findings in 11 Canadian ex-Ps.O.W from the far East who had suffered from varying degrees of nutritional neuropathy and Ps.O.W who had died in the subsequent 10 years from unrelated causes. Clinically, these presented a picture like that described by Scott-retrobulbar neuropathy, burning feet, signs of posterior column and peripheral nerve damage but no evidence of pyramidal tract damage. The histological findings were, most constantly, symmetrical demyelination of the posterior columns particularly the fasciculus gracilis near the midline. There was no consistent abnormality of the peripheral nerves and no evidence of any inflammatory process. The lateral corticospinal tracts were intact. The optic nerves showed the same degenerative demyelinisation particularly in the papillo-macular fibres. This also occurred in patients who had no temporal pallor but all had some deterioration in visual acuity. Similar cord changes have been described by, Spillane and Scott (1945) in German Ps.O.W. from North Africa and by Ransome (1944) in one case from Malaya. But none of these postmortem neurological records come from patients who had signs of pyramidal tract damage. The syndrome described by Fisher and originally described by Crawford and Reid. (1947) in Ps.O.W. from Hong Kong was also seen in Malayan prison camps (Graves, 1947; Cruickshank, 1946 (b) and 1952); and in the Dutch East Indies (Smitskamp, 1947; Hobbs and Forbes, 1946). In addition, in Changi Camp Singapore over 60 patients were observed presenting the clinical features of a lateral corticospinal tract lesion with or without a retrobulbar neuropathy and, in a few, signs of posterior column damage as well. Postmortem examinations were carried out on 4 of these.

Unfortunately, the cords and brains could only be examined microscopically but the white matter in the region of the pyramidal tracts at all levels of the cord and brain showed areas that had a sago grain translucency and was slightly depressed below the level of the cut surface. There was no evidence of inflammation and it is reasonable to assume that these represented demyelinisation of the tracts. Pieces of brain and cord were preserved in the hope that they might subsequently be examined microscopically but they were confiscated by the Japanese (Graves, 1947; de Wardener and Lennox, 1947; Denny-Brown, 1947; Cruickshank, 1946 (a) and 1952). It is probable that the aetiology was closely related if not identical with that of the other cord, retrobulbar and 8th nerve lesions which were also observed. The clinical picture they presented is virtually the same as that of the cases under discussion.

The Aetiology and Differential Diagnosis

These cases must initially be differentiated from well recognised conditions that may present with almost identical clinical features. These are local lesions of the cord such as intra or extra-meduallary tumours, acute or chronic inflammatory lesions due to tuberculosis, syphilis, pyogenic organisms or viruses, vascular lesions from primary disease of the cord vessels or compression of the vessels by protrusions resulting from degenerative lesions of the vertebral column particularly the disc in the cervical region (this is commonly seen in Jamaica), disseminated sclerosis, subacute combined degeneration and the rarer cord degenerations of unknown origin such as amyotrophic lateral sclerosis, syringomyelia, Charcot-Marie Tooth disease *etc*.

Local lesions of the cord can only be excluded by the selectivity of the damage on clinical assessment, negative

X-ray findings with and without contrast media in the spinal canal, the absence of gross abnormality in the C.S.F. and no signs of a block, negative C.S.F. serological tests for syphilis and, finally, on the natural history of the process from onset and while under observation. It is important to record that 2 cases originally regarded as belonging to this syndrome subsequently developed localising signs and at surgery a meningioma was found in one and a stenosing local meningitis of uncertain aetiology in the other. Only time will tell whether or not some of the other cases are also in this category.

Most of the cases, particularly those in the younger age groups with an associated retrobulbar neuropathy when seen for the first time, in Europe or North America would be regarded as cases of multiple sclerosis but the course of the disease is entirely different. There are no periods of progression and regression and the maximum damage in nearly all cases is reached within a few months of onset and it remains static thereafter. Nystagmus, dysarthria and intention tremor, so frequently associated with disseminated sclerosis, do not occur. Moreover, multiple sclerosis (in the experience of all physicians in the West Indies) is extremely rare in the Negro population. All the cases in this series were of Negro or predominantly Negro stock. Perhaps this syndrome is multiple sclerosis in a modified form but it seems most unlikely. It differs from classical multiple sclerosis in too many ways.

The high incidence of positive V.D.R.L. and Wasserman tests for syphilis (or yaws) in the community raises the question of the part played by these diseases. The blood was positive in thirty per cent of the cases although in none was the C.S.F. positive as such cases were excluded from the series. Most of these tests were weakly positive only three being positive in over 1:4 dilutions. Thirty per cent positivity is within the range of 12 – 44% positive tests (average 22%) in the different parishes in the island. In view of the negative C.S.F. Wasserman and the relative severity of the lesion in most cases, it is extremely unlikely that syphilis or yaws is, if at all, more than a minor contributory factor. Subacute combined degeneration of the spinal cord as a complication of pernicious anaemia can be ruled out by the normal blood findings in the great majority of cases. A megaloblastic marrow was present in three cases with a histamine fast achlorhydria. One of these, a man of 49 may well be true pernicious anaemia with subacute combined degeneration. His blood responded well and rapidly to B_{12} but there was no improvement in the neurological signs. The other two were women aged 24 and 29 years at the time of onset of the neurological symptoms. One developed a bilateral 8th nerve deafness. The diet of one was rated as fair and her megaloblastic marrow rapidly returned to normal with B_{12}. The other's diet was poor and her blood picture returned to normal with hospital diet alone. In neither was there any improvement in the neurological symptoms. Neither can, in the circumstances, be regarded as true pernicious anaemia with subacute combined degeneration.

An interesting finding is the presence of a histamine fast achlorhydria in 25 of 90 cases in which a fractional test meal was done. No control figures are available for a similar group of the population without the neurological disorder. An analysis of the age, diet and type of lesion in these 25 cases (see Table 3) gives little significant information except that the average age is 49, i.e. nine years above the overall average. The possible significance, if any, of this finding will be discussed later when the evidence for a dietary cause of the syndrome is reviewed.

The cerebrospinal fluid examination in 93 cases showed no increase in cells in any, some increase in protein (over 30 mg%) in 62, with a paretic curve in 20 of these. This can be accounted for on the basis of any demyelinising process and has no specific significance.

Fifty cases out of 70 in which liver function tests were done showed some abnormality. In most cases, this was a reversal of the albumin: globulin ratio but in some there was also abnormality of the flocculation tests and depression of the cholinesterase. As with the incidence of a histamine fast achlorhydria, this finding will have to be compared with results for a similar population group without neurological findings before any possible significance can be attached to it but the histamine fast achlorhydria may point to defective digestion and absorption and the abnormal liver function tests may indicate a disturbance of normal metabolic processes either the result of poor or unbalanced nutrition, the presence of a dietary toxic factor or repeated chronic infection. No gross histological change of significance was demonstrable in the liver biopsy specimens from 19 cases.

The Nature of the Lesion

If it is accepted that in these cases a specific local lesion or infection of the nervous system is ruled out a cause must be sought which will account for the selectivity of the damage. No satisfactory explanation is forthcoming but there are many interesting possibilities which require further consideration.

The two neurons bearing the brunt of the damage: the upper motor neuron and the first sensory neuron for proprioception are the largest, longest and most heavily myelinated in the nervous system. They must therefore carry a heavy metabolic "load". Moreover phylogenetically they are the two most recent tracts of the cord. These factors may account for their succeptibility to damage.

The factor or factors responsible presumably interfere with the metabolism of these neurons leading firstly to a biochemical lesion which to a varying degree results in structural damage. Whether this latter occurs first in the myelin sheath or in the axis cylinder is speculative but such scanty data as is available from experimental and post-mortem material indicates that demyelinisation is the earlier change followed by axon and then cell body degeneration. Unfortunately, as yet, little is known biochemically of the controlling elements in myelin metabolism. Does the lesion

occur primarily in the cell body leading secondarily to myelin and then to axon degeneration with the most peripheral part of the neuron suffering first and most, or does the primary defect occur in the metabolism of the myelin and axon at the periphery? Scott (1918) found that the maximal degeneration in the posterior columns was in the cervical and upper thoracic region which would support the concept that the part of the neuron most distant from the cell body suffers most. In his material, this was also the case in the spino-cerebellar tracts. No information of this kind is available for the corticospinal tracts as these seem to have been spared in both his and Fisher's cases. Experimental work by Swank (1940) in chickens with thiamine also supports the latter hypothesis. The axis cylinder and myelin sheath cannot survive without the parent cell body and nucleus but we do not know exactly what metabolic activities are dependent on this integrity. There is no doubt that the peripheral part of the neuron has metabolic needs of its own as it cannot survive without a blood supply but what exactly these needs are, is still being sought by neuro-physiologists.

The specific factor or factors responsible for the disturbed metabolism and damage to these neurons is also unknown. There are many interesting possibilities. In the first instance, individual tissue succeptibility must be postulated on account of the scattered but scanty distribution of the syndrome in the community and environmental and racial factors may play their part. In addition, there are two main possibilities:-

(1) deficiency of substances essential for nerve cell metabolism as a result of (a) interference with the blood supply (vascular spasm or disease) (b) failure of the body to produce them either by synthesis or from store as in pernicious anaemia (c) insufficient amounts being present in the gastrointestinal tract or absorbed therefrom (d) the presence of anti-enzymes or analogues in the gut or tissues.

(2) toxic factors, extrinsic or intrinsic, including the allergies. Any combination of the above factors may be operative in a given case.

As the syndrome in most cases occurs in persons with a relatively poor dietary, e.g. Ps.O.W, deficiency of an essential factor is likely. On the other hand, most of the patients in this series were in good physical condition and had no overt signs of any recognised deficiency syndrome. We know that a specific deficiency of Vit. B_{12} can produce selective lesions of the posterior and lateral columns indicating their succeptibility to damage. There is ample experimental evidence in rats, chickens, dogs, pigs and men that thiamine, riboflavine, pyridoxine and pantothetic acid deficiency individually or in combination can produce nerve cell damage particularly in the first sensory neuron for proprioception (Zimmerman et al., 1937; Phillips and Engel, 1938; Shaw and Phillips, 1941; Street et al., 1941 (a and b); Vilter et al, 1953; Wintrobe et al., 1942). Deficiency of other substances, for example certain amino acids may also produce the lesion. A specific toxic factor in the diet for example, in the bush teas so popular in Jamaica is another possibility. This is known to be the case in lathyrism, which closely resembles this syndrome but posterior column damage, retrobulbar neuropathy and 8th nerve deafness are not reported. Substances have now been isolated in pure form from the lathyrus family of the legumes which will produce nervous system damage in rats and mice as well as skeletal and vascular lesions. These are nitrile compounds and the one on which most work has been done is Beta-aminopropiononitrile – a concentration of 1:500 000 producing lesions within a week (Ponseti, 1954).

There is thus still much work both experimentally and by clinical observation to be done on this problem particularly in a hunt for a specific toxic dietary factor, More knowledge on the fundamental metabolism of myelin is required and more information is wanted on the incidence of the syndrome in other Caribbean territories and in tropical countries.

SUMMARY

The clinical features of 100 cases of a neuropathic syndrome observed in the University College Hospital of the West Indies over a period of 3½ years are described.

The four main features are:

(a) upper motor neuron damage (93)
(b) damage to the first sensory neuron
(c) retrobulbar neuropathy
(d) eighth nerve deafness

The onset is from the second to the sixth decade and may be sudden or gradual. The sex incidence is equal. Maximum incapacity occurs within a few months and the disease thereafter appears to be stationary. No pathological material has yet been available for study but the nature of the lesion and the possible causes are discussed.

The diet of the patients varied from good to very poor but few showed overt signs of vitamin deficiency or malnutrition.

A dietary factor is possibly responsible but there is no definite evidence of this.

RESUMEN

Se describen las caracteristicas clinicas de 100 casos de un sindrome neuropatico observadas en el Hospital del University College durante un plazo de 3½ anos. Las cuatro caracteristicas principles son:

(1) dano sufrido en el neuroma motor superior (93)
(2) dano sufrido en le primer neuroma sensorio
(3) neuropatia retrobulbar
(4) sordera del octavo nervio

Se registra el acceso de la enferndad entre la segunda y la sexta decada; puede ser repentino o paulatino. La incidencia en los dos sexos es igual. La incapacidad maxima ocurre dentro de unos pocos meses y después de esto la enfermedad parece establecerse en un estado estatica. Todavía no se han conseguido materiales patológicas para un

estudio detenido; no obstante se describe la naturaleza de la lesión y las causas que pueden ocasionarla.

La dieta de los pacientes variaba de buena a malísima pero pocos manifestaban senales evidentes de deficiencia de vitaminas ni de desnutrición. Puede que sea responsable un agente dietario pero de esto no tenemos evidencia definitiva.

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