J. Roy. Coll. Phycns Lond.

# Metabolic Neuropathy

P. K. THOMAS, DSc, MD, FRCP, Department of Neurology, Royal Free Hospital, London

Disturbances of peripheral nerve function are encountered in a wide variety of generalised metabolic disorders. The more important 'metabolic neuropathies' are those associated with diabetes, porphyria, amyloidosis and uraemia. Neuropathy occurring in relation to liver disease has recently attracted some attention (Knill-Jones *et al.*, 1972). This paper is confined to some observations on three of these disorders.

## AMYLOID NEUROPATHY

There is a certain sameness about many peripheral neuropathies. That associated with amyloidosis is one of the more interesting forms because of a number of individual features. It may occur in relation to sporadic cases of primary amyloidosis or amyloidosis secondary to multiple myeloma. Of particular importance is the familial occurrence of amyloidosis with peripheral nerve involvement. Such cases have been described with especial frequency in Portugal (Andrade, 1952), where 173 families are known to exist with nearly 700 affected individuals (Andrade, 1970). The Portuguese disease is inherited in an autosomal dominant manner. The condition begins in the lower limbs, usually between the ages of 25 and 35, with a distal impairment of pain and temperature appreciation. Autonomic features occur early and include postural hypotension, impotence in the male, and disturbances of bladder and bowel function. Dissociated sensory loss appears later in the arms, and an atrophic weakness and loss of other sensory modalities distally in the limbs subsequently ensues. The tendon reflexes tend to be preserved until quite late in the evolution of the disease. The peripheral nerves may become thickened. The condition is slowly progressive and is fatal in 10 to 12 years. Families with similar features have been described in Japan (Araki *et al.*, 1968).

A somewhat different clinical picture was encountered in families reported from Indiana (Rukavina *et al.*, 1956) and Maryland (Mahloudji *et al.*, 1969) in which the earliest neurological manifestations consist of sensory symptoms of median nerve distribution. Sensory loss later spreads more widely in the upper limbs and involves the lower legs. The inheritance is again of autosomal dominant pattern.

At the Royal Free Hospital, we have had experience of two sporadic cases

and one familial case, of Greek origin, in which the clinical features resembled those of the Portuguese patients. Sural nerve biopsies showed extensive amyloid deposits, mainly within the fascicles and, often, perivascular in distribution. Our results confirmed the selective loss of small myelinated nerve fibres reported by Dyck and Lambert (1969), which could be related to the dissociated pain and temperature sensory loss. Although degenerative changes were frequently observed in unmyelinated axons, the gross loss of such nerve fibres found by Dyck and Lambert was not evident.

There has been considerable discussion on whether or not amyloid deposits produce nerve damage by ischaemia (Kernohan and Woltman, 1942), in view of their frequent perivascular distribution, or by a direct mechanical effect (Chambers *et al.*, 1958). It has recently been claimed that, in familial cases, nerve fibre damage is detectable before the appearance of amyloid deposits, leading to the suggestion that the deposition of amyloid is a secondary phenomenon (Coimbra and Andrade, 1971). Although ischaemia could be responsible for the loss of small myelinated nerve fibres before those of larger calibre, no infarcts have been observed in nerves. It is also difficult to see how ischaemia could lead to early damage to unmyelinated axons.

Direct distortion of nerve fibres by amyloid deposits has been observed repeatedly (Chambers *et al.*, 1958; Dyck and Lambert, 1969). However, under experimental conditions, the largest myelinated nerve fibres are affected first by pressure, the C fibres being the most resistant. In our material, we have found a definite tendency for the amyloid fibrils to be deposited in relation to the basal lamina (basement membrane) of the Schwann cells associated with unmyelinated axons. Such deposits appear to be directly related to cell damage.

### URAEMIC POLYNEUROPATHY

The clinical features of the peripheral neuropathy that may be observed in chronic renal failure (Asbury *et al.*, 1963) closely resemble those of the neuropathy encountered in patients under treatment by periodic haemodialysis, suggesting that both are the consequence of the same metabolic disturbance. The incidence of neuropathy in the various reported series was reviewed by Robson (1968), who found an overall incidence of 44 per cent. Our initial experience at the Royal Free Hospital was gained from a group of 20 consecutive cases where the incidence of peripheral nerve disturbance was 75 per cent. Of these, in all except three who had a persistent sensori-motor neuropathy, there was a sensory neuropathy which cleared within a few weeks of the start of dialysis. The incidence now appears to be noticeably less, this probably being related to differences in case selection and dialysis procedures. As a

measure of the present situation, we have assessed the occurrence of neuropathy in a consecutive series of 54 patients under treatment by the Renal Unit of St Bartholomew's Hospital, London. When examined at the start of dialysis, about half were normal, a quarter showed abnormalities of nerve conduction without symptoms or signs of neuropathy, and a quarter had clinical evidence of neuropathy (Table 1). It has been suggested (Tyler, 1968; Thomas *et al.*,

TABLE 1. Chronic haemodialysis cases: status at start of dialysis

| | |
|---|---|
| Normal | 28 |
| Conduction defect only | 14 |
| Neuropathy | |
| signs only | 4 |
| with symptoms | 8 |
| | 54 |

1971) that neuropathy is more liable to occur in males. This was not our experience in the present series, in which the distribution of male and female cases with peripheral nerve involvement fairly accurately reflected the distribution in the whole series (Table 2).

TABLE 2. Chronic haemodialysis cases: sex distribution

| | Male | Female |
|---|---|---|
| Whole series | 35 | 19 |
| Neuropathy | | |
| conduction defect only | 10 | 4 |
| clinical neuropathy | 11 | 7 |
| | 21 | 11 |

TABLE 3. Chronic haemodialysis cases: symptoms of neuropathy

| | |
|---|---|
| Sensory only (distal numbness and paraesthesiae; 'restless legs') | 6 |
| Motor only (distal weakness and wasting) | 2 |
| Mixed sensori-motor | 5 |

The symptoms of uraemic neuropathy are of some interest and have been listed in Table 3, which includes those cases with neuropathy present at the

start of dialysis in this series, together with others in whom neuropathy developed during the course of treatment. In 6, the features were purely sensory, with distal paraesthesiae and sensory loss, usually mainly in the lower limbs. In these cases, as is already known to occur in uraemic neuropathy (Callaghan, 1966), nocturnal 'restless legs' was sometimes a prominent symptom. In 5, the sensory features were combined with distal weakness, again most marked in the legs. Finally, in 2 cases, a virtually pure distal motor neuropathy was encountered. This pleomorphic clinical picture raises the possibility that multiple factors may be involved in the origin of neuropathy.

The values for motor nerve conduction velocity in the peroneal nerve in this series at the time of the start of dialysis is given in Table 4; the degree of the

TABLE 4. Chronic haemodialysis cases: motor nerve conduction velocity (m/sec) in peroneal nerve

| | |
|---|---|
| Dialysis cases | |
| with neuropathy | 30·4 ± 6·1 |
| without neuropathy | 41·1 ± 3·8 |
| Controls | 49·7 ± 7·1 |

reduction is comparable to that of other series. It will be seen that there is an appreciable reduction in velocity in the cases with clinical evidence of neuropathy, and, even in those who were clinically normal, velocity is moderately reduced. The occurrence of subclinical neuropathy has been documented by Preswick and Jeremy (1964) and others.

A nerve biopsy was obtained from only one case in this series, a patient with a pure motor neuropathy (Case 10, Thomas *et al.*, 1971). A sural nerve biopsy was entirely normal. In cases with sensory or mixed sensory and motor involvement, axonal breakdown has been observed with a moderate degree of secondary demyelination (Dyck *et al.*, 1971; Thomas *et al.*, 1971). The axonal changes are maximal at the periphery (Asbury *et al.*, 1963) and the disorder can therefore be considered as an example of a 'dying-back' neuropathy.

The cause of uraemic neuropathy is unknown, but the improvement with dialysis (Konotey-Ahulu *et al.*, 1965) suggests that a retained metabolite of low molecular weight is responsible. Although alterations in plasma magnesium levels affect conduction velocity in patients under treatment by dialysis (Fleming *et al.*, 1972), claims that magnesium is involved in the genesis of neuropathy have not been confirmed (Hollinrake *et al.*, 1970).

Robson (1968) showed that there is an abnormal elevation of the plasma pyruvate concentration following a glucose load in uraemic subjects. As this occurs with thiamine deficiency, the possibility that the neuropathy results from an interference with thiamine metabolism has to be considered. Yet the abnormality of pyruvate metabolism is not corrected by thiamine administration, nor does the neuropathy respond to massive vitamin supplementation. We examined erythrocyte transketolase activity in patients under treatment by dialysis (Pryse-Phillips, 1970), but this was normal, whether or not the patients had evidence of neuropathy. Since then a report has appeared (Lonergan *et al.*, 1971) claiming that transketolase activity is depressed in renal failure and suggesting a relationship to the occurrence of neuropathy. We therefore have examined a further series of patients with severe chronic renal failure not under treatment by dialysis (Roberts, 1972) and have again found normal transketolase activity, as have other workers (Kopple *et al.*, 1972). The disturbance of pyruvate metabolism remains unexplained, but it still perhaps offers a clue as to the origin of the neuropathy.

## THE CLASSIFICATION OF DIABETIC NEUROPATHY

The variegated nature of diabetic neuropathy has been evident since the early descriptions at the end of the last century (Pryce, 1893), and a wide variety of classifications has been advocated. The search for valid subgroups is more than just a taxonomic exercise, since the definition of entities within the wide range of manifestations that is observed may help in the elucidation of causative factors. Undoubtedly there is a considerable overlap between the different categories, so much so that some authorities have concluded that no satisfactory subdivision is possible (Pirart, 1965) or that diabetic neuropathy is a single entity (Greenbaum, 1964).

Peripheral nerve disorders, in general, can be divided into two categories. Firstly, there are symmetrical polyneuropathies which are usually the result of the operation of a process such as toxic, metabolic or deficiency states that act diffusely on the nervous system. Secondly, there are isolated peripheral nerve lesions (mononeuropathy) or multiple isolated lesions (multiple mononeuropathy), where localised factors such as pressure, vascular lesions or infiltrations are often implicated. Applying this to diabetic neuropathy (Table 5), it is evident that the common sensory neuropathy is an example of a symmetrical polyneuropathy. What is not so often realised is that autonomic involvement is of this nature, but this is clearly evident in the precise symmetry of the anhidrosis recorded by Goodman (1966). Moreover, there appears to be a close association between the symmetrical sensory polyneuropathy and autonomic neuropathy. In the careful study by Osuntokun (1971), in 71 cases of diabetic

TABLE 5. Classification of diabetic neuropathy

| |
|---|
| **Symmetrical polyneuropathy** |
| sensory polyneuropathy |
| autonomic neuropathy |
| **Mononeuropathy and multiple mononeuropathy** |
| cranial nerve lesions |
| isolated peripheral nerve lesions |
| 'diabetic amyotrophy' |

autonomic neuropathy, 65 had an associated symmetrical sensory or sensorimotor polyneuropathy.

The isolated cranial nerve palsies or isolated peripheral nerve lesions are examples of mononeuropathies, and the asymmetrical and patchy involvement in 'diabetic amyotrophy' suggests that this syndrome can be included as an example of a multiple mononeuropathy.

It is evident that vascular lesions are important in the origin of isolated oculomotor nerve palsy (Asbury *et al.*, 1970) and diabetic amyotrophy (Raff *et al.*, 1968). The symmetrical nature of the sensory and autonomic syndromes indicates that it is here more appropriate to seek a diffusely acting metabolic cause. The two types of pathological process may possibly interact, so that nerves compromised by a metabolic disturbance may be more susceptible to pressure lesions or to vascular insults, this contributing to the overlap between the various syndromes.

*Acknowledgements*

I wish to thank Dr W. Cattell and Dr L. R. I. Baker, Renal Unit, St Bartholomew's Hospital, and Dr J. F. Moorhead, Renal Unit, Royal Free Hospital, for their co-operation.

*This article is based on a paper read at the College Conference on Metabolic Aspects of Disease held in Cardiff in September 1972.*

*References*

Andrade, C. (1952) *Brain*, **75**, 408.
Andrade, C. (1970) *Arthritis and Rheumatism*, **1**, 902.
Araki, S. (1968) *Archives of Neurology* (Chicago), **18**, 593.
Asbury, A. K., Aldredge, H., Hershberg, R. and Fisher, C. M. (1970) *Brain*, **93**, 555.
Asbury, A. K., Victor, M. and Adams, R. D. (1963) *Archives of Neurology* (Chicago), **8**, 413.
Callaghan, N. (1966) *Neurology (Minneapolis)*, **16**, 359.
Chambers, R. A., Medd, W. E. and Spencer, H. (1958) *Quarterly Journal of Medicine*, **27**, 207.
Coimbra, A. and Andrade, C. (1971) *Brain*, **94**, 207.
Dyck, P. J., and Lambert, E. H. (1969) *Archives of Neurology* (Chicago), **20**, 490.
Dyck, P. J., Johnson, W. J., Lambert, E. H. and O'Brien, P. C. (1971) *Mayo Clinic Proceedings*, **46**, 400.
Fleming, L. W., Lenman, J. A. R. and Stewart, W. K. (1972) *Journal of Neurology, Neurosurgery and Psychiatry*, **35**, 342.

Goodman, J. I. (1966) *American Journal of Medicine*, **41**, 831.
Greenbaum, D. (1964) *Brain*, **87**, 215.
Hollinrake, K., Thomas, P. K., Wills, M. E. and Baillod, R. A. (1970) *Neurology (Minneapolis)*, **20**, 939.
Kernohan, J. W. and Woltman, H. W. (1942) *Archives of Neurology and Psychiatry, Minneapolis*, **47**, 132.
Knill-Jones, R. P., Goodwill, C. J., Dayan, A. D. and Williams, R. (1972) *Journal of Neurology, Neurosurgery and Psychiatry*, **35**, 22.
Konotey-Ahulu, F. I. D., Baillod, R., Comty, C. M., Heron, J. R., Shaldon, S. and Thomas, P. K. (1965) *British Medical Journal*, **2**, 1212.
Kopple, J. D., Dirige, O. V., Jacob, M., Wang, M. and Swendseid, M. E. (1972) *Transactions of the American Society for Artificial Internal Organs*, **18**, 250.
Lonergan, E. T., Semar, M. S., Sterzel, R. B., Treser, G., Needle, M. A., Voyles, L. and Lange, K. (1971) *New England Journal of Medicine*, **284**, 1399.
Mahloudji, M., Teasdall, R. D., Adamkiewicz, J. J., Hartmann, W. H., Lambird, P. A. and McKusick, V. A. (1969) *Medicine, Baltimore*, **48**, 1.
Osuntokun, B. O. (1971) *The Neurology of Diabetes Mellitus in Nigerians*. M.D. Thesis, University of London.
Pirart, J. (1965) *Diabetes*, **14**, 1.
Preswick, G. and Jeremy, D. (1964) *Lancet*, **2**, 731.
Pryce, T. D. (1893) *Brain*, **16**, 416.
Pryse-Phillips, W. (1970) Unpublished observations.
Raff, M., Sangalang, V. and Asbury, A. K. (1968) *Archives of Neurology* (Chicago), **18**, 487.
Roberts, A. H. (1972) Unpublished observations.
Robson, J. S. (1968) In *Symposium: Some Aspects of Neurology* (ed. R. F. Robertson) p. 74, Edinburgh: Royal College of Physicians of Edinburgh.
Rukavina, J. G., Block, W. D., Jackson, C. E., Falls, H. F., Carey, J. H. and Curtis, A. C. (1956) *Medicine, Baltimore*, **35**, 239.
Thomas, P. K., Hollinrake, K., Lascelles, R. G., O'Sullivan, D. J., Baillod, R. A., Moorhead, J. F. and Mackenzie, J. C. (1971) *Brain*, **94**, 761.
Tyler, H. R. (1968) *American Journal of Medicine*, **44**, 734.

---

### Drinking for Health

Andrew Boorde (1490–1549) considered that 'A good cook is half a physician. For the chief physic (the counsel of a physician excepted) doth come from the kitchen.' Naturally, he was also concerned about drinking. 'Water', he thought, 'is not holesome sole by itself, for an English man. Water is cold, slow and slack of digestion.' 'Ale for an English man is a natural drink . . . Beer is made of malt, of hops and water: it is a natural drink for a Dutch man. And now of late days it is much used in England to the detriment of many English men; for the drink is a cold drink; yet it doth make a man fat and doth inflate the belly, as it doth appear by the Dutch men's faces and bellies.'

He felt better about wine, for 'moderately drunken it doth quicken a man's wits, it doth comfort the heart, it doth scour the liver; specially, if it be white wine, it doth rejoice all the powers of man.' When it came to milk he chose his words with care. 'Milk is nutritive, and doth humect and moisten the members and doth mundify and cleanse the entrails, and doth alleviate the pain of the lungs and the breast; but it is not good for them the which have gurgulations in the belly'.