The neurological manifestations of malabsorption

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Summary

The clinical and pathological findings in patients with neurological disorders in association with disordered function of the small intestine, in particular coeliac disease, are outlined. The possible significance of the abnormalities of pyridoxine, tyrosine and tryptophan metabolism are considered in relation to bipterin derivatives and their relevance to neurological dysfunction.

MALABSORPTION syndromes are clinical disorders arising from disturbances of small intestinal function although pernicious anaemia is not usually included in this category. The principal disorders are coeliac disease, post-gastrectomy states and small intestinal diverticulosis. Tropical sprue and regional enteritis both with a high incidence of low levels of serum vitamin B₁₂ are also included and, for completeness, Whipple's disease which occasionally presents with a neuropathy must also be included (Maizel Ruffin and Dobbins, 1970).

In some of these disorders, the neurological manifestations of vitamin B₁₂ deficiency will occur, sometimes with peripheral nerve, spinal cord or cerebral symptoms being the first evidence. They are well recognized as occurring in post-gastrectomy states where the incidence of vitamin B₁₂ deficiency 10-15 years after operation is high (Williams *et al.*, 1969) and small intestinal diverticulosis (Cooke *et al.*, 1963). They do not, however, appear to occur in tropical sprue, regional enteritis or in coeliac disease despite the high incidence of low serum levels of vitamin B₁₂. However, when such neurological disorders have been excluded, there remain many patients with post-gastrectomy states, small intestinal diverticulosis or with coeliac disease (Cooke and Smith, 1966) in whom cerebral manifestations, spinal cord lesions or peripheral neuropathy appear unrelated to any obvious aetiological factor such as vitamin B₁₂ deficiency, platybasia and osteomalacia (Hurwitz and Banerji, 1972), Wernicke's syndrome, chronic electrolyte depletion or the myopathy of vitamin D deficiency (Smith

and Stern, 1967). Much of the work concerning these neurological complications has been done with coeliac disease, but there is little clinical difference to be detected in the clinical situations in other disorders of the small intestine. In passing, it should be noted that this type of neurological disorder displays surprisingly close similarity to carcinomatous neuropathy.

To consider first the manifestations of organic nerve involvement (and secondly the mental and psychological associations), the neuropathy affects the limbs principally and the legs in particular with numbness, tinglings, pain, weakness and unsteadiness of gait. Indeed, ataxia rapidly becomes the major symptom. Although the arms are less commonly affected, some patients are unable to write steadily or undo buttons. Ankle jerks are lost early: evidence of posterior column involvement is marked in the legs whilst sensory impairment of glove and stocking type is frequent. Ataxia is usually of the postural type but cerebellar signs are present in some. Attacks of unconsciousness occur in many patients.

The pathological findings are striking (Cooke and Smith, 1966; Cooke, Johnson and Wolff, 1966). In two thirds of the author's patients, there was atrophy and focal loss of neurones, sufficiently marked in some cases for the cortical atrophy to be noted macroscopically, the nerve cells being replaced by a retiform network of glial fibres and in some there was also astrocyte hypertrophy accompanied by neuronal degeneration. Spinal cord lesions tend to be patchy and non-systematized with spongy demyelination of the posterior and lateral columns with variable degrees of axonal degeneration and little gliosis. In the peripheral nerves, there was collateral branching and re-innervation with diffuse swellings of the terminal axons. On electron microscopy, these terminal axons showed gross disorganization of the internal structure with breaking up of presynaptic membrane, multivesicular and electron-dense bodies, degenerated mitochondria and a curious 'frog-spawn' cytoplasm (Cooke *et al.*,

1966). Patchy demyelination of the peripheral nerves has also been observed (Binder, Solitare and Spiro, 1967).

The course of the disorder seems to be slowly progressive, although the occasional patient does achieve remission. In a few, the course is such as to suggest an ascending polyneuritis of infective origin leading even to death from respiratory failure (Cooke and Smith, 1966; Cooke, 1976).

The mental and psychological abnormalities associated with diseases of the small intestine were considered by Goldberg (1970) to be many and varied but not significantly different from those encountered in the general population. It is nevertheless widely accepted that there are changes of mood and personality in the untreated coeliac, particularly children, mainly of a depressive nature and that this is profoundly influenced by the gluten load (Daynes, 1956; Paulley, 1959; Sheldon, 1959). There is little evidence recorded that mental deficiency is more frequent in children of coeliac parents but a gluten-free diet was associated with a striking improvement in mental capacity in one such patient in the author's series. Schizophrenia has also been related to possible gluten intolerance in that discharge rates of schizophrenics on a cereal-free and milk-free diet are significantly better than those for patients not so treated (Dohan and Giasberger, 1973). The incidence of schizophrenics in the author's series is not known for certain but it is clear from experience of three such patients that a gluten-free diet plays a significant part in bringing about remissions of their abnormal mental state (Cooke, 1976). This can be sometimes frustrating for in one such patient relapse from diet leads to mental relapse which then leads to rigid refusal to return to a gluten-free diet.

The occurrence of severe pathological changes in the brain makes it probable that psychiatric abnormalities may well be associated with such changes. Amongst those coeliac patients who have been followed to post-mortem, there were some with progressive mental deterioration and who had been diagnosed as suffering from an organic dementia, and who had evidence of cerebral atrophy. Two similar patients are at present under treatment with a gluten-free diet and their progressive mental deterioration appears to have been halted for the last four years (Cooke, 1976).

The cause of these neurological complications is by no means clear and is probably multifactorial. The possibility that infection is the basis for these diffuse neuropathic lesions cannot lightly be dismissed. The clinical course in some patients was highly suggestive. Destruction of Purkinje cells with sparing of others is seen in some viral infections such as poliomyelitis or the transmissible spongiform,

slow, virus-type encephalopathies (Gajdusek and Zigas, 1957). There is undoubtedly some defect in the immunological status of coeliac patients although there is no evidence to suggest that they are more prone to ordinary infections than the general population. Nevertheless the possibility remains.

Vitamin B₁₂ deficiency does not appear to play a significant role other than in the well recognized and specific entities. Attempts have been made to incriminate folic acid deficiency as a primary cause of neuropathy (Grant, Hoffbrand and Wells, 1965; Strachan and Henderson, 1967; Ahmed, 1972; Fehling *et al.*, 1974). The evidence put forward is by no means convincing and the consensus of opinion is that folic acid is not a primary factor. Pyridoxine deficiency has also been suggested (Cooke and Smith, 1966). Low levels of serum pyridoxine have been found in a large proportion of coeliacs tending to revert to normal on treatment with a gluten-free diet (Morris, Ajdukiewicz and Read, 1970; Cooke, 1976). There is also a low excretion of 4-pyridoxic acid in the urine of many coeliac patients (Cooke, 1968). Furthermore, pyridoxine deficiency has been related to over-utilization in order to counteract a defect in tryptophan metabolism (Kowlessar, Haeffner and Benson, 1964). Even so, there is no convincing evidence that coeliac patients with neuropathy benefit significantly from pyridoxine therapy so that the possibility that these defects reflect dysfunction of other metabolic pathways must be considered.

Over the past few years, increasing interest has been displayed in the bipterin compounds and their role in human metabolism, particularly in the production of neurotransmitters. They can now be measured with great sensitivity and precision by the requirement of the organism *Crithidia fasciculata* for these compounds as a growth factor. The compounds concerned are bipterin, 7,8-dihydrobipterin, 5,6,7,8-tetrahydrobipterin and neopterin which can be separated by thin layer chromatography, gas chromatography and high voltage electrophoresis. They act as co-factors to phenylalanine hydroxylase and to dihydropteridine reductase in the hydroxylation of phenylalanine to tyrosine. This same co-factor system is used in normal tissue for the hydroxylation of dihydrophenylalanine (laevodopa) in the synthesis of the amine neurotransmitters, dopamine, noradrenaline and adrenaline and also in the hydroxylation of tryptophan to 5-hydroxytryptophan in the synthesis of serotonin. Any condition that reduced the amount of active tetrahydrobipterin would interfere with the synthesis of neurotransmitters and create neurological syndromes (Smith, Clayton and Wolff, 1975). It is therefore of interest that Blair, Leeming and Melikian (1978) have demonstrated significantly low serum levels of

Crithidia factor in severe senile dementia and also in untreated coeliac patients. The levels are also significantly lowered in schizophrenia (Leeming *et al.*, 1976). Such observations are particularly significant when related to those by Kowlessar *et al.* (1964) on the disturbance in tryptophan metabolism and to the defects in tyrosine metabolism reported by Boscott and Cooke (1954).

The difficulties of the interpretation of the significance of serum levels concerned in complex biochemical processes needs no emphasis. The findings in phenylketonuria emphasize the importance of these compounds in producing organic neurological defects, but much more remains to be done in defining the normal physiological pathways and role of these compounds. As far as disorders of the small intestine are concerned, they offer some hope for explaining the defects in pyridoxine, tyrosine and tryptophan utilizations that have been noted in coeliac disease and the neurological complications that occur.

References

- AHMED, M. (1972) Neurological disease and folate deficiency. *British Medical Journal*, **1**, 181.
- BINDER, H.J., SOLITARE, G.B. & SPIRO, H.M. (1967) Neuromuscular disease in patients with steatorrhoea. *Gut*, **8**, 605.
- BLAIR, J.A., LEEMING, R.J. & MELIKIAN, V. (1978) (Personal communication).
- BOSCOTT, R.J. & COOKE, W.T. (1954) Ascorbic acid requirements and urinary excretion of p-hydroxyphenylacetic acid in steatorrhoea and macrocytic anaemia. *Quarterly Journal of Medicine*, **23**, 307.
- COOKE, W.T. (1968) Adult coeliac disease. In: *Progress in Gastroenterology*, (Ed. by Glass, G.B.) vol. 1, p. 299. Grune & Stratton, New York.
- COOKE, W.T. (1976) Neurologic manifestations of malabsorption. In: *Handbook of Clinical Neurology* (Ed. by Vinken, J. and Bruyn, G.W.), vol 28, p. 225, North-Holland Publishing Co., Amsterdam.
- COOKE, FONE D.J., COX, E.V., MEYNELL, M.J. & GADDIE, R. (1963) The clinical and metabolic significance of jejunal diverticula. *Gut*, **4**, 115.
- COOKE, W.T., JOHNSON, A.G. & WOLF, A.L. (1966) Vital staining and electron microscopy of the intramuscular nerve endings in the neuropathy of adult coeliac disease. *Brain*, **89**, 663.
- COOKE, W.T. & SMITH, W.T. (1966) Neurological disorders associated with adult coeliac disease. *Brain*, **89**, 683.
- DAYNES, C. (1956) Bread and tears. Naughtiness, depression and fits due to wheat sensitivity. *Proceedings of the Royal Society of Medicine*, **49**, 391.
- DOHAN, F.C. & GIASBERGER, J.C. (1973) Relapsed schizophrenics: earlier discharge from hospital after a cereal-free milk-free diet. *American Journal of Psychiatry*, **130**, 683.
- FEHLING, C., JAGERSTAD, M., LINDSTRAND, K. & ELMQUIST, K. (1974) Folate deficiency and neurological disease. *Archives of Neurology*, Chicago, **30**, 263.
- GAJDUSEK, D.C. & ZIGAS, V. (1957) Degenerative disease of the central nervous system in New Guinea. *New England Journal of Medicine*, **257**, 974.
- GOLDBERG, D. (1970) A psychiatric study of patients with diseases of the small intestine. *Gut*, **11**, 459.
- GRANT, H.C., HOFFBRAND, A.V. & WELLS, D.G. (1965) Folate deficiency and neurological disease. *Lancet*, **ii**, 763.
- HURWITZ, L.J. & BANERJI, N.K. (1972) Basilar impression of the skull in patients with adult coeliac disease and after gastric surgery. *Journal of Neurology, Neurosurgery and Psychiatry*, **35**, 92.
- KOWLESSAR, O.D., HAEFFNER, L.J. & BENSON, G.D. (1964) Abnormal tryptophan metabolism in patients with adult coeliac disease with evidence of deficiency of vitamin B₉. *Journal of Clinical Investigation*, **43**, 894.
- LEEMING, R.J., BLAIR, J.A., GREEN, A., MELIKIAN, V. & O'GORMAN, D.J. (1976) Biopterin derivatives in human body fluids and tissues. *Journal of Clinical Pathology*, **29**, 444.
- MAIZEL, H., RUFFIN, J.M. & DOBBINS III, W.O. (1970) Whipple's disease. A review of nineteen patients from one hospital and a review of the literature since 1950. *Medicine*, Baltimore, **49**, 175.
- MORRIS, J.S., AJDUKIEWICZ, A.B. & READ, A.E. (1976) Neurological disorders in adult coeliac disease. *Gut*, **17**, 549.
- PAULLEY, J.W. (1959) Emotion and personality change. Aetiology of steatorrhoea. *American Journal of Digestive Diseases*, **4**, 352.
- SHELDON, W. (1959) Celiac disease. *Pediatrics*, **23**, 132.
- SMITH, I., CLAYTON, B.E. & WOLFF, O.H. (1975) New variant of phenylketonuria with progressive neurological illness unresponsive to phenylalanine restriction. *Lancet*, **i**, 1108.
- SMITH, R. & STERN, G. (1967) Myopathy, osteomalacia and hyperparathyroidism. *Brain*, **90**, 593.
- STRACHAN, R.W. & HENDERSON, J.G. (1967) Dementia and folate deficiency. *Quarterly Journal of Medicine*, **36**, 189.
- WILLIAMS, J.A., HALL, G.S., THOMPSON, A.G. & COOKE, W.T. (1969) Neurological disease after partial gastrectomy. *British Medical Journal*, **2**, 210.