Familial amyloidosis with gastrointestinal neuropathy

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Among the various forms of primary amyloidosis, there is one type that seems more or less confined to Portuguese people. First described by Corino de Andrade, a Portuguese neurologist, in 1952, and intensively investigated in Portugal during the last few years, some cases have been observed in other countries. It is a familial and hereditary disease, affecting both sexes and following a slow, progressive, and always fatal course. The chief signs and symptoms are: (1) peripheral neuropathy, with motor sensitivity and trophic changes, especially in the lower limbs; (2) sexual impotence; and (3) digestive disturbances. The aetiology is unknown and pathology shows deposits of amyloid, predominantly affecting the peripheral nerves. A definite diagnosis may be obtained by biopsy of the skin or a peripheral nerve, or, more easily, by peroral biopsy of the digestive tract (Monterio, 1963).

The digestive syndrome included in this curious disease is particularly interesting. The initial complaints of the patient are usually neurological or gastroenterological, or both, and the digestive disturbances are often serious and even disabling. My data are based on the observation of 16 patients. Diagnosis was always proved by biopsy of the skin and/or the digestive tract.

The nature of complaints is not always the same, but a similar picture emerges from the great majority of cases. The patient first notices a moderate degree of constipation, more and more marked as time goes by. Then a curious cycle tends to become established. The bowels do not move for some days—sometimes 15 or 20—during which stage the patient complains of progressive epigastric fullness and abdominal distension, anorexia, and a bad taste in the mouth. Foul eructations and borborygmi herald the transition to the second phase of the cycle, characterized by an explosive diarrhoea, usually lasting one to three days, with many loose stools—up to 20 a day—throughout the day and night, without blood, often with mucus. Pain is not frequent, but urgency is usual and incontinence not rare. With the occurrence of diarrhoea, the patient is relieved of fullness

and distension, and his appetite improves, but, at the same time, he feels very weak. Nausea and vomiting are observed in a few cases.

Physical examination does not contribute very much. Abdominal distension, slight diffuse tenderness, and spontaneous or induced borborygmi are the most frequent signs. Peristalsis is more often hypoactive. Digital examination of the rectum almost always shows some decrease in the tone of the anal sphincter, which not rarely is completely relaxed. Proctosigmoidoscopy is often difficult to complete, because the patency of the anus does not allow the patient to retain air. The mucosa is normal, but in many cases the rectal walls are collapsed, forming folds as if the sigmoidoscope were already in the sigmoid.

Stool examination is usually normal, although some patients appear to digest muscle fibres poorly. Gastric analysis with the Ewald test revealed, in most patients, hypochlorhydria or even achlorhydria (responsive to histamine); in many instances, food remnants could be aspirated with the fasting sample. Uropepsin was low in almost every patient. Liver function tests did not substantiate any consistent derangement. Blood count may be normal, but most cases have a slight anaemia and sometimes leucopenia. Plasma proteins, chloride, sodium, potassium, and calcium were almost always normal.

The oral glucose tolerance test usually gave a flat curve, and the d-xylose test was below normal in 33.3% of cases. Intestinal absorption was also studied with radioisotopes, using triolein, oleic acid, risa and vitamin B₁₂. Anomalies were not striking.

Patients had a complete radiological survey of the digestive tract, but a barium enema was often difficult because of anal incontinence. The colon was either normal or slightly dilated and hypotonic. Examination of the oesophagus, stomach, and duodenum did not show any lesions, but in most patients the stomach and duodenum were hypotonic, the duodenal cap was dilated, and gastric emptying was delayed, sometimes very markedly. The small bowel was essentially normal.

Peroral biopsy of the digestive tract was done in 15 of the 16 patients, using the Crosby capsule. A crystal violet stain showed amyloid deposits in 13 patients. Eighteen biopsies were taken altogether, 11 from the jejunum, six from the stomach, and one from the duodenum. At every site it was possible to find amyloid, mainly deposited in the muscularis mucosae, also frequently in the vessels of the thin piece of submucosa included in the specimen.

Intestinal malabsorption, due to the amyloid deposits in the bowel, is the traditional explanation for digestive symptoms in amyloidosis (Ribeiro do Rosario, 1961). The clinical, laboratory, radiological, and histological investigations presented above lead to a different interpretation, at least in this peculiar form. It is my opinion that intestinal malabsorption, although it may contribute to the picture, is not its main cause. In fact, clinical signs and symptoms of deficiency states are unusual, and plasma proteins and electrolytes are normal. Diarrhoea comes for short periods, separated by longer periods of constipation. Stool examination is normal or shows only slightly defective digestion of muscle fibres, which may be explained by the decrease in gastric secretion. Abnormalities in the absorption tests are not conspicuous and, when present, may be explained, at least in part, by the delay in gastric emptying. In this series, an abnormal result in the d-xylose test was corrected when sugar was introduced through a duodenal tube. The microscopic picture of the jejunum is essentially normal, except for the deposits of amyloid, which lie mainly in muscle. Moreover, it is not possible to establish any correlation between the amount of amyloid deposited and the severity of the digestive trouble. It is my belief that the digestive syndrome of familiar amyloidotic polyneuropathy is mainly due to a complex motor disturbance of the digestive tract. The clinical picture is suggestive of a predominant stasis, with fulness, distension, foul eructations, borborygmi, and constipation present most of the time. This stasis is probably in the

stomach, as shown by gastric analysis and radiology. For instance, it is frequently very difficult to pass a tube or the Crosby capsule beyond the stomach. It is conceivable that gastric stasis usually, in a hypochlorhydric or achlorhydric patient, can cause decomposition products that would explain the foul eructations and, through irritation of the bowel, the period of diarrhoea that ensues. Dynamic abnormalities of the bowel could also contribute to the picture. The motor disturbance is probably due to amyloidotic lesions of the autonomic nervous system (although infiltration of the muscle itself may play a part). In fact, in this peculiar form of primary amyloidosis, deposits of amyloid are predominantly seen in the nervous tissue and necropsy of fatal cases shows the vagi to be infiltrated. Most patients are hypochlorhydric or achlorhydric and, in many cases, the response of gastric secretion to insulin was poor or even negative. Moreover, in these patients, other signs of disturbance of the autonomic nervous system may be seen: sooner or later, impotence is certain, and postural hypotension may be seen.

SUMMARY

In familial amyloidotic polyneuropathy, although certain other factors, such as malabsorption or decreased gastric and possibly pancreatic secretion, may play a part, the main cause of the digestive syndrome is a complex motor disturbance of the digestive tract, essentially due to amyloidotic infiltration of the nerves of the digestive tract.

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