Encephalitis with myoclonus in Whipple's disease

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In 1907, Whipple described a man of 36 with progressive loss of weight, asthenia, steatorrhea, gastrointestinal disorder, and polyarthritis. At necropsy, deposits of fat and fatty acids were seen in the intestinal wall and the mesenteric lymph nodes. In 1966, Tengström and Werner were able to review 143 cases of Whipple's disease reported between 1950 and 1965.

In 1949, Black-Schaffer demonstrated the presence of PAS-positive material in the macrophages of the intestinal mucosa and in the mesenteric lymph nodes of cases of Whipple's disease. Sieracki and Fine (1959) called these cells SPC cells (sickle-formed-particle-containing cells) because of the shape of the inclusions. Sieracki (1958) had mentioned their presence in lymph nodes and throughout the reticuloendothelial system. The diagnosis of Whipple's disease can now be confirmed by a peroral jejunal biopsy, by mesenteric lymph node biopsy, and sometimes by the biopsy of a peripheral lymph node.

Tengström and Werner (1966) mentioned neurological signs briefly in 6% of the 143 cases they reviewed, and Sieracki, Fine, Horn, and Bebin (1960) had described subependymal nodules of SPC cells in the brain of two patients, but neither patient had neurological signs or symptoms. In the present case (and in 11 other reports), the central nervous system had clearly been involved in Whipple's disease, and the neurological signs were so marked that the other clinical signs were relatively neglected.

CASE HISTORY

The patient was a 68-year-old woman. There was no family history of nervous disease. She had migratory distal arthritis for three years and episodes of intolerance to fat, loss of 20 kg weight, and asthenia during the last two years of life.

In June 1966, when aged 67, she began to suffer from attacks of pain 'like electrical discharges' beginning in the right external auditory canal and spreading to the right periorbital area. The pain was often preceded by redness of the ear and tickling of the auditory canal. These attacks lasted two hours and were accompanied by increased salivation. There was no trigger zone. The attacks became more frequent and in September they were associated with involuntary contractions of the masseters and the muscles of the right upper limb.

As the pain could not be controlled by analgesics, alcohol was injected into the right trigeminal ganglion and this gave relief. The muscular twitches however became more frequent and more severe.

From 25 October to 29 November 1966, the patient was admitted to the University Clinic of Louvain. She suffered from bilateral heart decompensation. She had an iron deficiency anaemia, the haemoglobin being 9.85 g%, the haematocrit 32%, and the serum iron level 31 μg%. This anaemia was attributed to diverticulosis of the colon, which was demonstrated radiologically.

Laboratory investigations showed ESR 85 mm in one hour, WBC 16,000/cu.mm (neutrophils 83%), total serum protein concentration: 6.31 g% (electrophoretic fractions: albumin 31%, α1 globulin 7.5%, α2 15%, β 21%, γ 25.5%), C-reactive protein test: + + +, Wahler-Rose test negative, antistreptolysin titre normal. The serum levels of urea, sodium, potassium, chlorides, alkaline phosphatase, and transaminases were normal. Flocculation tests (Takata, Kunkel, thymol), glucose tolerance test, urine microscopic examination were normal, as was gastric analysis. The cerebrospinal fluid contained 1 cell/cu.mm and 21 mg protein/100 ml.

The optic fundi showed narrowing of the arterioles and the optic discs were pale; the visual fields were full. Cochlear and vestibular examinations were normal.

The electroencephalogram showed normal alpha rhythm (9 c/s) without paroxysmal features.

Examination in January 1967 confirmed the existence of right facial and scapulo-humeral myoclonic jerks, which were now also observed in the pharynx and larynx. Their amplitude was variable, but often so marked as to prevent the patient from sleeping. The trigeminal neuralgia had disappeared. The tendon reflexes were more brisk on the right side. Her general state had deteriorated: she had lost 5 kg in weight in the two preceding months. From January 1967 the myoclonic jerks became more and more violent and affected also the left leg.

In October 1967 she was admitted to the Department of Medicine of Ixelles Hospital. She was fully conscious and well orientated in time and space. She appeared very asthenic and emaciated. Myoclonic jerks affected the right half of the face, the pharynx, the larynx, the right half of the diaphragm, the flexor muscles of the right upper

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limb, the muscles of the anterior and lateral aspects of the calf, and the flexors of the toes of the right leg. These were rhythmic (65/min), synchronized, and of such an amplitude that the whole body shook and the patient was in a very exhausted state.

Other myoclonic jerks, of smaller amplitude, were present in the muscles of the anterior and lateral aspects of the calf and in the flexors of the toes of the left leg. Their rhythm was similar to that on the right side of the body but they were not synchronized. Other neurological signs observed were a right 6th nerve palsy and slight bilateral rigidity of all the muscles of the limbs, increased by contralateral voluntary movements.

A few days after admission, bilateral ophthalmoplegia and difficulty in swallowing appeared. The electroencephalogram showed artefacts due to the muscular twitchings, but after intravenous injection of diazepam, these muscular artefacts disappeared and the record appeared normal. Severe cardiac decompensation and bilateral lung infection prevented further investigation. The patient died 10 days after this second admission to hospital. She was then 68 years old.

Necropsy

This was carried out seven hours after death and revealed diverticulosis of the colon and marked enlargement of the mesenteric lymph nodes (up to 2 cm in diameter) many of which were infiltrated with fat. Portions of the organs were embedded in paraffin and sections were stained by haematoxylin and eosin and by periodic acid Schiff reagents.

The myocardium, lungs, pancreas, adrenals, and kidneys were normal. The spleen presented collections of histiocytes containing granular PAS-positive inclusions. The cortex and medulla of the mesenteric lymph nodes were honeycombed by fat spaces. Their structure was modified by the presence of numerous foamy histiocytes and multinucleated giant cells whose cytoplasm contained PAS-positive material, of homogeneous, granular, and rod-shaped appearance. The mucosa of the small and large intestine exhibited foamy cells with finely granular, PAS-positive material.

The histological picture of the intestine, lymph nodes, and spleen was that seen in Whipple's disease.

Nervous system (I.B. 199/67) No naked-eye lesion was seen in the brain. The anterior horns of the spinal cord were markedly congested. The brain was fixed in 12% formal saline. Sections of the brain and spinal cord were stained by Spielmeyer, Holzer, PAS, Sudan III, and cresyl-violet methods.

Numerous subpial and perivascular amyloid bodies were found in the leptomeninges, the cerebral cortex, and the white matter. The caudate and lenticular nuclei were normal. The amygdaloid nucleus contained a great number of nodules of histiocytes and a few perivascular areas of lymphocytic cuffing (Figs. 1 and 2). The rhinencephalon presented many nodules of histiocytes in the olfactory striatum and in the internal parolfactory area. The thalamus was normal. Similar nodules were also found in the reticular and compact zones of the substantia nigra, the peri-aqueductal grey matter (Fig. 3), the pretectal nucleus, the peripenduncular nucleus, and in Dark-schevitsch's nucleus. Similar nodules and perivascular


FIG. 2. The same at higher magnification to show the histiocytic perivascular proliferation. Frozen section, cresyl-violet, × 200.

FIG. 3. Periaqueductal grey matter. A nodule and a lymphocytic cuffing above the medial longitudinal fascicle. Frozen section, cresyl-violet, × 75.
cuffings were noted in the grey matter around the 4th ventricle, the reticular nuclei (n. pontis centralis oralis, n. parabrachialis lateralis, n. pontis centralis caudalis, n. gigantocellularis, n. parvoceullaris, according to Olszewski and Baxter’s nomenclature, 1954) (Fig. 4), the locus coeruleus, the decussation of the brachia conjunctiva, the lateral lemnisci, the vestibular nuclei, and the motor nuclei of the trigeminal nerve.

Similar lesions were found in the medulla (vestibular nuclei, n. medullae oblongatae centralis, subnuclear dorsalis and subnuclear ventralis, nucleus of the 5th cranial nerve, nucleus gracilis and nucleus cuneatus, supraspinal nuclei). A few nodules were present in the inferior olivary nucleus. Many amyloid bodies were found in the white cerebellar matter and in the hilum of the dentate nucleus. Only one small inflammatory zone was noted in the ventral part of the dentate nucleus. Lesions were observed in all the grey matter of the spinal cord and consisted of microglial nodules, perivascular cuffing by lymphocytes, congestion, and petechial haemorrhages.

The nodules were centred around capillaries whose endothelial cells were swollen. The nodules consisted of histiocytes whose cytoplasm contained many PAS-positive granules and rod-shaped particles. These cells correspond with the 'SPC cells', as described by Sieracki et al. (1960). Marked proliferation of rod-shaped microglial cells occurred and extended often into the contiguous parenchyma. A moderate degree of astrocytic proliferation was observed around the lesions. Perivascular cuffing by lymphocytes and monocytes was also noted in the zones where nodules of histiocytes were numerous.

To summarize, nodules filled with SPC cells were present in the rhinencephalon, the tegmentum of the brain-stem, and the grey matter of the spinal cord.

One of us has studied with De Groodt-Lasseel the ultrastructural features of the CNS lesions, the results of which are separately reported (De Groodt-Lasseel and Martin, 1969).

We have been able to find bacteria and different stages of disintegration with collection of residual walls in histiocytes (Fig. 5a and b).

**DISCUSSION**

The previously reported neurological lesions in Whipple’s disease included apathy, stupor, and dementia in six cases. In one of these (Lampert, Tom, and Cumings, 1962) this led to the diagnosis of Alzheimer’s disease. Extrapyramidal signs were observed by Schwartzová, Schwartz, and Marek (1967), and numbness of the face in one of those described by Smith, French, Gottsmann, Smith, and Wakes-Miller (1965).

Signs of brain-stem involvement are often mentioned and include external and/or internal ophthalmoplegia (five patients) and sometimes nystagmus. Myoclonic jerks were described by Lampert et al. (1962), Krücke and Stochdorph (1962), Smith et al. (1965), but in none of these cases were they as spectacular as in our patient. Obstructive hydrocephalus (due to a stenosis of the aqueduct of Sylvius caused by a granular ependymitis) was reported by Krücke and Stochdorph (1962) and paraplegia due to spinal cord involvement by Koudouris, Stern, and Utterback (1963). The electroencephalogram was normal in three cases, while in four there were diffuse slow waves. Krücke and Stochdorph (1962) noted an increase in the white cells in the cerebrospinal fluid in case 1; in six other cases it was normal.

The frequency of granular ependymitis (see Table) and the existence of PAS-positive material in the leptomeninges (Schwartzová et al., 1967) indicate that a careful study of the CSF after centrifugation or sedimentation and a careful search for SPC cells should be made after staining by the PAS reagents.

Cerebral biopsy is not justified, as the lesions are irregularly distributed and because a peroral jejunal biopsy is the best way to diagnose Whipple’s disease.

Today, many ultrastructural studies of the visceral lesions in Whipple’s disease have repeatedly led to the discovery of bacteria in the intestinal mucosa and the mesenteric lymph nodes (Chears and Ashworth, 1961; Mopert, Bianchi, and Bühler, 1968).

Ashworth, Douglas, Reynolds, and Thomas (1964) have shown that the PAS-positive granules and rods correspond with the intracytoplasmic accumulation of residual bacterial bodies. The PAS-positivity is very likely due to the presence of mucopolysaccharides in the bacterial membrane. Indeed we have been able to demonstrate the presence of bacteria and of residual bacterial bodies (accumulated in the histiocytes) in CNS nodular

**FIG. 4.** Lymphocytic cuffing in the reticular formation of the brain-stem. Frozen section, cresyl-violet, × 55.
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**FIG. 5a and b** (By courtesy of Professor De Groodt-Lasse). Ultrastructural study of a nodule located in the periaqueductal grey matter. **a** = bacteria with a clearly recognizable double membrane, cut either longitudinally or transversely (see arrows, × 30,000). **b** = on the right of the picture, bacteria with rather well-preserved features; on the left, residual walls emptied of their contents (see arrows, × 30,000). Formalin fixation, washing in collidine buffer and OsO4 post-fixation, thin sections made with an ultramicrotome Reichert OMu2, contrasting with uranylacetate and lead citrate, examination with Siemens Elmiskop 1.
lesions. Their perivascular location allows us to suggest a haematogenous dissemination of the microorganisms.

Finally, it is well known that the most frequent cause of skeletal and palato-pharyngo-oculo-dia-phragmatic myoclonus is a vascular lesion of the brain-stem, as stressed by several works of the French neurological school—for example, Gallet (1927), Van Bogaert and Bertrand (1928), Guillaum and Mollaret (1931, 1932), and Alajouanine, Thurel, and Hornet (1935). However, other causes must also be considered, as illustrated in our patient who developed myoclonus due to lesions of the brain-stem, and this was a very dramatic feature of the present case.

SUMMARY

The report deals with a patient of 68 who developed a neurological syndrome lasting one and a half years, characterized initially by trigeminal neuralgia, followed by skeletal myoclonus and then by an ophthalmoplegia. Emaciation and anaemia were other striking features of the disease.

Necropsy revealed Whipple's disease. The central nervous system showed a nodular encephalitis with PAS-positive material. The amygaloïd nucleus, the rhinencephalon, the subthalamus area, the tegmentum of the brain-stem, and the grey matter of the spinal cord are selectively involved. A clinical and pathological comparison is carried out with 11 other cases in the literature.

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