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Progressive Myoclonic Epilepsy (Unverricht Type) with Atypical Lafora Bodies

Case Report

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Summary. A patient with advanced progressive myoclonic epilepsy (Unverricht type) with Lafora bodies is presented. Although the clinical history and symptoms were classical, the regional distribution of the cerebral involvement differed from the classical picture: the corpora mamillaria, the nucleus subthalamicus, and the nucleus ruber, which are normally reported to be spared, contained multiple Lafora bodies, whereas the lateral geniculate body, which is usually involved, was intact. The number of inclusions per cell, up to 25, was extremely high and correlated with the marked cortical atrophy and the prolonged clinical course. Using electron microscopy, type I and type II Lafora bodies were found, but the latter lacked the typical filamentous ultrastructure in the peripheral zone. The lack of visceral Lafora bodies in this case suggests that liver, muscle, and skin biopsies, which are widely used for the diagnosis, may lead to false negative results and cannot always replace a stereotactic brain biopsy. The differential diagnosis of polyglucosan bodies is emphasized.

Key words: Progressive myoclonic epilepsy – Lafora bodies – Polyglucosan bodies

Introduction

Progressive myoclonic epilepsy (PME) with Lafora bodies (Lafora disease) is a rare, lethal disease which is caused by a presumed inborn error of carbohydrate metabolism by which a substance belonging to the group of amylopectin-like polysaccharides is abnormally stored. The enzyme deficiency which leads to the accumulation of polyglucosan bodies is unknown. The clinical course is characterized by generalized tonic-clonic seizures, myoclonus, ataxia, dysarthria, and progressive dementia. Girls are more afflicted than boys (Seitelberger 1968). Classically, two clinical types of the disease have been observed. The Unverricht type is characterized by a rapid, severe course beginning before age 15, with death occurring usually before the age of 25. The second type (Lundborg) shows a more protracted, less severe course and begins clinically between the ages of 16 and 20, with survivals up to age 40 observed. A clinically similar disorder, Baltic myoclonus, occurs, but is not a polyglucosan storage disease since inclusion bodies are not found. Its biochemical basis is also uncertain (Koskiniemi et al. 1974). The diagnosis of PME of either type is based on the clinical features and on the histological demonstration of the typical inclusion bodies in the brain, liver, or ducts of the cutaneous sweat glands. The latter two tissues are more conveniently biopsied than the brain and are frequently used to establish the diagnosis (Carpenter and Karpati 1981). As is illustrated by the present case, these extra-CNS inclusions may be absent, even in an advanced case.

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Case Report

A female patient, born in 1954, with an unremarkable family history, showed severe disturbances in childhood development with enuresis nocturna until the age of 9. Her achievements in school increasingly deteriorated, and from the age of 12 there was progressive disintegration of her personality. At 13 years of age the first psychomotor seizure occurred with perceptual illusions suggesting a temporal lobe origin, and these seizures were usually followed by generalized tonic-clonic convulsions. In 1972, she was hospitalized permanently with suspected Lafora disease. Therefore, the skin was biopsied, but no inclusion bodies typical for PME were seen in multiple sweat or sebaceous glands (Carpenter and Karpati 1981). A stereotactic brain biopsy was performed and light microscopy showed multiple typical intraneuronal Lafora bodies in a section of cerebral cortex. Clinically, the patient then showed increasingly frequent generalized seizures, myoclonus, ataxia, dysarthria, and progressive dementia. The EEG showed generalized sharp-wave complexes correlating with the myoclonic attacks. Epileptic foci were found over both temporal lobes with accentuation on the right. The somatosensory evoked potentials were giant. In the following years the patient progressively deteriorated and increasingly lost contact with the outside world. Because of the wishes of her family, every effort was made to extend the patient's life and she was fed permanently via a gastric tube. In 1982, at the age of 28, the now quadriparetic patient developed vigil coma. The patient died of pneumonia in 1984 at the age of 30 years, 17 years after the first onset of seizures.

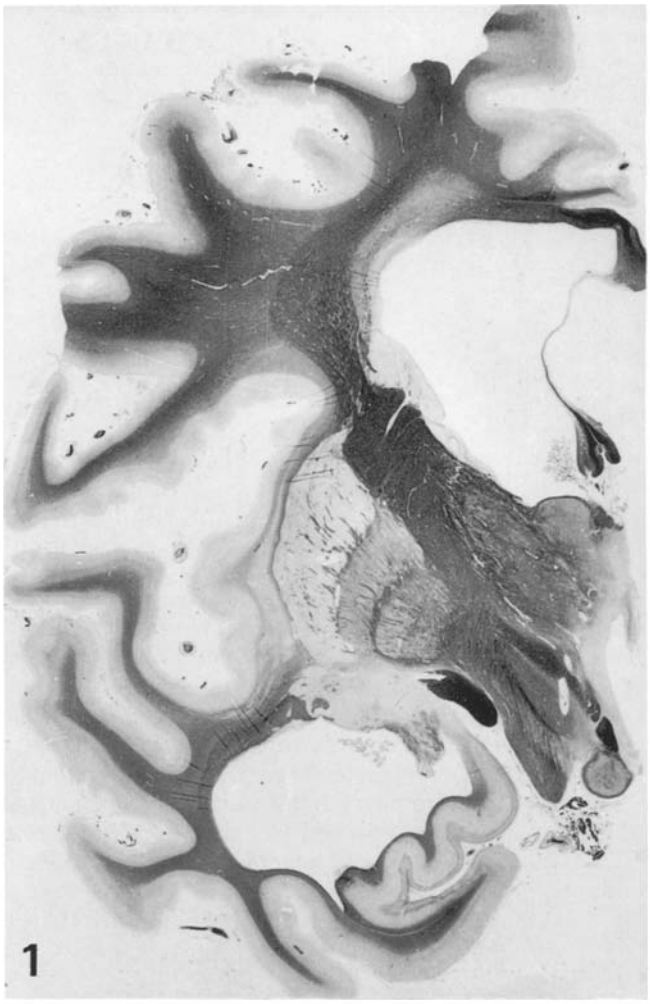

Fig. 1. A frontal section at the level of the mammillary bodies showing severe cortical atrophy, but general sparing of the basal ganglia and thalamus. Luxol-Nissl × 2.1

General Autopsy Findings

The lung showed diffuse acute and organizing pneumonia, obstructive bronchiolitis, and pleural effusions. There were small areas of centrilobular hepatic necrosis. Inclusions resembling Lafora bodies were not seen in multiple sections of the heart, liver, pancreas, or cutaneous sweat glands.

Neuropathology Gross Findings

The 606 g brain showed severe bilateral cortical atrophy. The gyri temporales medius and inferior and gyrus postcentralis were somewhat spared (see Fig. 1). The circle of Willis, cranial nerves, brain stem, and cerebellum were macroscopically unremarkable. Frontal sections showed fibrous thickening of the leptomeninges and a hydrocephalus ex vacuo. There was shrinkage of the centrum semiovale, while the basal ganglia and the diencephalic structures were unremarkable. The substantia nigra was depigmented. There was secondary shrinkage of the pontine and medullary pyramidal tracts and the cerebellar peduncles.

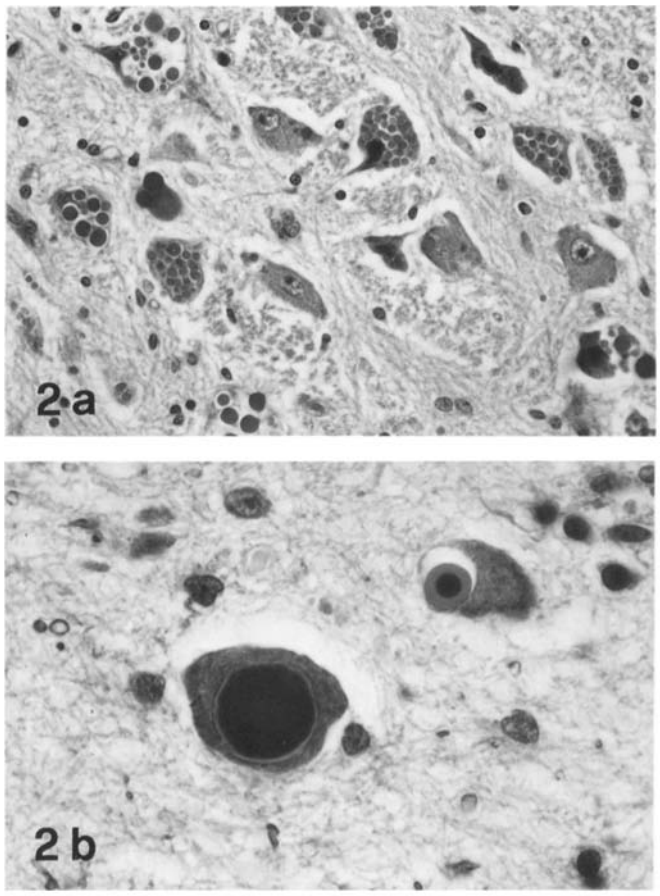

Fig. 2a, b. Single and multiple intraneuronal Lafora bodies in the pons. **a** Some cells contain as many as 25 intracytoplasmic inclusions. Hematoxylin-eosin × 250. **b** Note the prominent dark central core in the inclusion at top right. Luxol-Nissl × 600

Neuropathology Microscopic Findings

Single and multiple (up to 25) inclusion bodies with and without a darker eosinophilic core were found in the neuronal cytoplasm and, with much less frequency, extracellularly and intraaxonally. Their size varied from 1 to 35 μm (see Fig. 2). The staining pattern of the inclusion bodies in the present case is shown in Table 1. Immunohistochemical stains for glial fibrillary acidic protein, neuron-specific enolase, neurofilament, and S-100 protein were negative. The inclusion bodies diffusely involved the cerebral cortex which also showed neuronal loss and reactive gliosis. The 3rd and 5th cortical layers were predominantly affected. Diffusely distributed intraneuronal inclusions were also seen in the striate body, the thalamic and subthalamic structures, the mammillary bodies, the substantia nigra, and in the cerebellar dentate nucleus. There were inclusions in all structures of the pontine base and tegmentum with the exception of the trigeminal nucleus. The same extensive involvement was noted in the medulla oblongata, where only the inferior olivary nuclei were free of inclusions, although neuronal loss and gliosis were present. The Ammon's horn contained inclusion bodies only in Sommer's sector and in the subiculum. The latter also showed a subtotal neuronal loss and reactive gliosis. The endplate and the resistant sector of Ammon's horn were intact, as were the corpus geniculatum laterale, and the Purkinje cells. Severe Wallerian degeneration was observed in the pyramidal tracts in the brain stem.

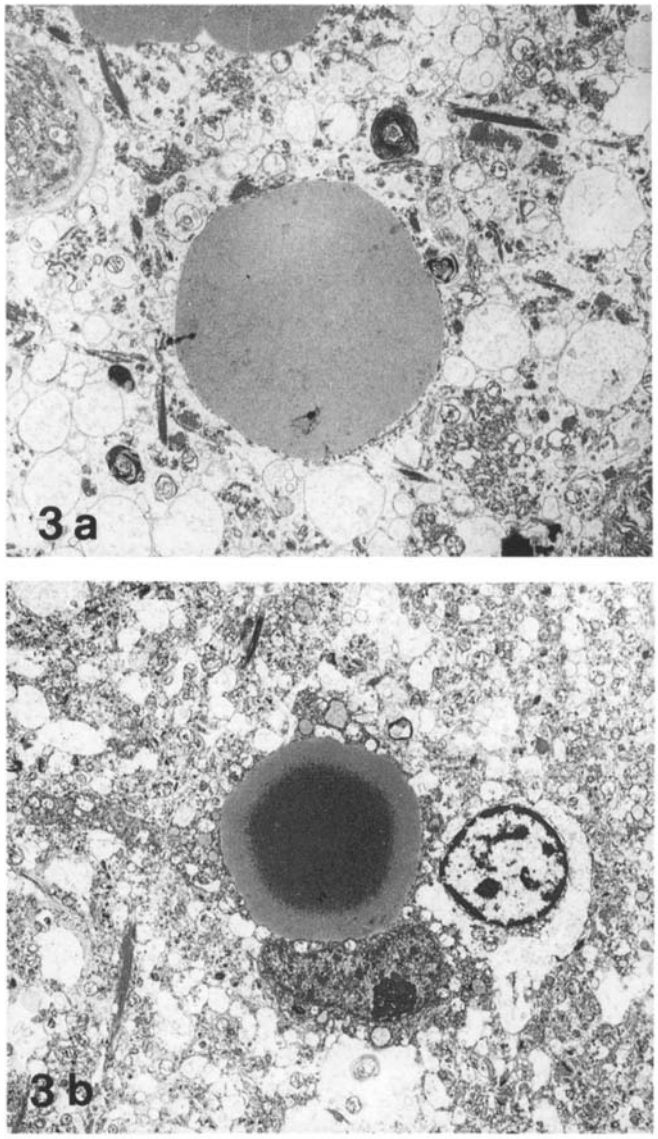

Fig. 3a, b. Electron microscopy of Lafora bodies. **a** The type I Lafora body shows a homogenous structure (× 16000). **b** An intraneuronal type II Lafora body shows a granulated core, but lacks the typical filamentous structure of the periphery. The neuronal nucleus is at the bottom (× 8000)

Electron Microscopy

Two types of Lafora bodies were seen (see Fig. 3). The first, corresponding to Lafora body type I, was a homogenous, spherical body consisting of lightly granulated material. The second, corresponding to type II, was spherical and had a dark, coarsely granulated core of varying size and a homogenous, amorphous periphery as seen in the first type. Filamentous structures were absent. A limiting membrane was not noted in either type.

Discussion

In the present case the clinical history and symptoms of the patient were characteristic of PME. The clinical course of the disease was severe and progressed rapidly. The relatively long survival of the comatose patient was due to extremely diligent hospital care and was presumedly responsible for the marked cerebral atrophy not usually seen in this disease. The diagnosis was based on the above clinical history and a stereotactic brain biopsy which showed classical Lafora inclusion bodies. The autopsy confirmed the diagnosis by demonstrating the same typical inclusions by light and electron microscopy (Dolman 1975; Kraus-Ruppert et al. 1970; Robitaille et al. 1980; Seitelberger 1968; Van Hoof and Hageman-Bal 1967).

Table 1. Histochemical properties of Lafora bodies in the present case

	Lafora body type I	Type II
H&E	Eosinophilic	Eosinophilic with lighter core
LN	Dark blue	Purple periphery, large blue core
PAS	Purple	Purple
AB	Light blue	Blue periphery, large red core
RETI	Positive	Positive
BEST	Positive	Positive periphery, negative core
TB	Negative	Negative
BB	Negative	Negative
HALE	Negative	Negative
MV	Light blue	Blue periphery, dark core
BO	Reddish brown	Reddish brown
HO	Dark blue	Dark blue halo, pale negative core
CR	Negative	Negative
GFAP	Negative	Negative
NSE	Negative	Negative
NF	Negative	Negative
S-100	Negative	Negative

Abbreviations: H&E: Hematoxylin-eosin, LN: Luxol-Nissl, PAS: Periodic acid-Schiff, AB: Alcian blue, RETI: Reticulin, BEST: Best-glycogen, TB: Turnbull, BB: Berlin blue, HALE: Hale's colloidal iron impregnation, MV: Methylviolet, BO: Bodian, HO: Holzer, CR: Congo red, GFAP: Glial fibrillary acidic protein, NSE: Neuron-specific enolase, NF: Neurofilament, S-100: S-100 protein

Lafora bodies were first described by Lafora and Glück in 1911 and belong to the group of polyglucosan bodies. The latter consist mainly of polymerized glucose, phosphate, and sulfate groups, and less than 5% protein (Seitelberger 1968; Yokoi et al. 1968). Polyglucosan bodies consist of three types: corpora amylacea, Bielschowsky bodies, and Lafora bodies. Histologically, ultrastructurally, and biochemically they are similar and cannot always in themselves be distinguished. The regional distributions in the CNS and the clinicopathological settings in which they are found are pathognomonic (for review see: Meldrum and Corsellis 1984; Robitaille et al. 1980). Corpora amylacea are found in normal ageing and Cori type IV glycogenosis (Andersen's disease, amylopectinosis) where, in either setting, they predominate in subpial, subependymal, and perivascular areas. Although corpora amylacea are classically found in astrocytic processes, it has been claimed that they can occur intraaxonally in the CNS, in axons of peripheral nerves within skeletal muscle, and within neuronal processes in the CNS (Anzil et al. 1974). Bielschowsky bodies are found exclusively in neurons in the lateral segment of the globus pallidus of patients with congenital choreoathetosis (double athetosis) combined with status marmoratus.

Polyglucosan bodies of the Lafora type are found in patients with PME. A few cases of amyotrophic lateral sclerosis with intraneuronal, Lafora-like inclusions have been described in the cerebrum and cerebellum, but not in the spinal cord, by Orthner et al. (1973) and Barz et al. (1976).

Because of the histological and immunohistochemical similarities between Lafora bodies and corpora amylacea, it has been difficult to establish conclusively the presence of Lafora bodies within astrocytes, although such a localization has been suggested. In his study in 1980, Robitaille claimed that Lafora bodies could be identified in astrocytes. However, Seitelberger (1968) in his review of 36 cases could not demonstrate inclusion bodies in either glial or mesenchymal cells. In the cortex where both astrocytes and neurons are intermingled, isolated Lafora bodies can often not be attributed to a specific cell type, and the possibility that they are evolved from astrocytes cannot be excluded. However the relative absence of Lafora bodies in the white matter, even in the present advanced case, suggests that, if astrocytic evolvement occurs, it is not frequent.

Using electron microscopy, type I Lafora body (homogenous structure) and type II (with a central core) could be identified, while type III (with a fissured, Y-shaped core) was not found. The absence of the filamentous, radiating arrangement in the peripheral zone in type II Lafora body was unusual in our case. Instead, the periphery contained finely granulated, PAS-positive material. Small type I inclusions corresponding to "dust-like particles" – staining with PAS, but not with H&E – could be seen focally in the neuropil. The lack of a limiting membrane, implicating an origin other than from lysosomes, was also in accordance with previous descriptions (Seitelberger 1968; Van Hoof and Hageman-Bal 1967). However, the inclusion bodies in our case were different from the so-called "atypical myoclonus bodies" described by Dastur et al. (1966). The latter were not polyglucosan bodies and showed a different staining pattern.

Although PME with Lafora bodies is often pictured as a disorder with predictible involvement, or noninvolvement, of various CNS regions, the present case makes it clear that the regional susceptibility is not constant. Thus, although the lateral geniculate bodies are usually heavily involved, and the mammillary bodies, the subthalamic nuclei, and the nucleus ruber are reported to be normally spared (Girard et al. 1975; Iwata 1973; Seitelberger 1968), the present case showed variations from this distribution. The involvement of generally spared regions may reflect the chronicity of the disease in the present case. However, the sparing of usually affected regions suggests that the disorder in different patients may manifest with involvement of different regions. In our case, the number of Lafora bodies per cell (up to 25) was extremely high and did not show the progressive reduction through the lower brain stem as is typically seen. This also may reflect the chonicity of the disease in this case. Severe atrophy of the brain, as in our case, was not observed by other authors (Meldrum and Corselli 1984; Seitelberger 1968).

Of clinical importance in the present case was the apparent absence of typical Lafora bodies in liver, muscle, and skin despite the very advanced stage of the disease. Biopsy of these tissues has been reported to be a reliable diagnostic tool and is widely used in the diagnosis of "Lafora disease" (Carpenter and Karpati 1981). The lack of visceral involvement in our case suggests that a negative result does not rule out the disease and that a brain biopsy may be necessary. Since the cerebral cortex is uniformely involved, this is an appropriate site for tissue sampling.

In summary, the clinical and morphological features of our case fit well into the entity of PME. However, the atypical morphological findings indicate the variability of the disease. The case also demonstrates that, although liver, muscle, and skin biopsies may be useful diagnostic tools, the absence of visceral Lafora bodies cannot rule out myoclonic epilepsy with multiple Lafora bodies in the CNS.

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