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CASE REPORT

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Infantile motor neuron disease with autonomic dysfunction and bunina bodies

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Abstract A 2-month-old girl developed motor neuron disease (MND) with autonomic disturbances and died at the age of 5 months. Neuropathological examination revealed Bunina bodies (BBs) in the lower motor neurons of the lumbar spinal cord. The significance of the presence of BBs and the classification of the MND in this child are discussed.

Key words Infant · Bunina bodies · Autonomic dysfunction · Motor neuron disease · Amyotrophic lateral sclerosis

Introduction

Whereas in adults the most common motor neuron disease (MND) is amyotrophic lateral sclerosis (ALS), in infants this is spinal muscular atrophy (SMA). To our knowledge, only two infants reported in the literature have been suggested to suffer from ALS [1, 2]. We describe an infant with MND, accompanied by autonomic disturbances, in whom Bunina bodies (BBs) were found in motor neurons of the lumbar spinal cord. While most clinical and neuropathological findings in this case are compatible with SMA, molecular genetic investigation was not indicative of SMA. Furthermore, several authors consider BBs to be specific for ALS [3–7]. The presence of autonomic disturbances is, however, regarded an exclusion criterion for ALS [8]. The classification of this MND is difficult and will be further discussed.

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Case report

The patient was the third child of healthy unrelated parents. Fetal movements had been normal. Because of intrauterine growth retardation and oligohydramnios, labor was induced at 37 weeks. The child, a girl, had Apgar scores of 8 and 9 after 1 and 5 min, respectively; birth weight was 2065 g (P3), length 44 cm (< P3) and occipitofrontal head circumference 33 cm (P30). After an unremarkable period of 2 months facial and respiratory muscle weakness and feeding problems developed. She was admitted to hospital at the age of 10 weeks because of pulmonary infection requiring mechanical ventilation.

Neurological examination revealed hypotonia, paresis and areflexia with abnormal plantar reflexes. On various occasions massive movements were observed. Later, apart from hypotonia of the proximal limb muscles and trunk, an increased tone of the leg muscles was noted (distal more than proximal). There was intermittent opisthotonus and abnormal posture characterized by extension of both arms with slight pronation and ulnar deviation of the hands and flexion of hips and knees with increased adductor muscle tone. The child could be designated ‘spastic’ rather than ‘floppy’. At 3 months, atrophy and contractures of the distal leg muscles and progressive external ophthalmoplegia were noted. Facial expressions were poor. Several well-documented episodes of hyperpyrexia, tachycardia and profuse sweating occurred with no apparent infectious cause and a positive histamine phosphate test, consistent with autonomic dysfunction. She remained ventilator dependent.

Analyses of blood (electrolytes, creatine kinase, phytanic-, lactic-, amino and very-long-chain fatty acids, lysosomal enzymes, liver and renal function), cerebrospinal fluid (cell count, proteins, glucose) and urine (amino and organic acids, purines and pyrimidines) were all normal. Blood lymphocytes showed no inclusion bodies. Botulism was ruled out and a prostigmine test was negative. Brain computer tomography and magnetic resonance imaging were normal, as were electroencephalographic registrations and brain stem evoked potentials. Electromyography of the abductor pollicis brevis, soleus, tibialis anterior and posterior, rectus femoris, deltoïdeus and biceps brachii muscles at ages of 3, 4 and 5 months was consistent with lower MND. The neuropathology of the quadriceps and soleus muscles and sural nerve is described below. Investigation of the survival motor neuron (SMN) gene (Dr. H. Scheffer, Dept. of Medical Genetics, University Hospital Gro-

ningen, The Netherlands) was normal. At 5 months another episode of hyperpyrexia (42.9° C) and tachycardia (up to 240 beats/min) occurred, this time followed by cardiac arrest despite resuscitation. Permission for autopsy was obtained, the abnormalities of which are described below.

Neuropathology

Muscle and nerve specimens

Muscle specimens were obtained at 3 and 5 months (quadriceps), the last one just 2 days before the patient died, and during autopsy (soleus). At 3 months muscle fibers were slightly smaller than normal; the checkerboard pattern of type I and II fibers was normal. At 5 months numerous atrophic fibers of both types were present in the quadriceps muscle. At autopsy, the soleus muscle showed an overwhelming presence of atrophic fibers of both types together with hypertrophic type I and II fibers. The diameter histogram was bimodal and the checkerboard pattern was disturbed. Ultrastructural examination of the quadriceps and soleus muscle, obtained by autopsy, revealed many fibers with redundant basal membrane loops, suggesting fast volume decrease of the muscle fibers. Biopsy samples from the sural nerve showed no quantitative or qualitative abnormalities.

Central nervous system

The brain and thoracic and lumbar spinal cord were available for further examination. The brain was proportional but small (weight after formalin-fixation 570 g, normal for age 725 ± 60 g). Dispersed neurons in the central nervous system showed hypereosinophilic change (consistent with hypoxic damage), associated with some pericellular vacuolation, but without gliosis or microglial proliferation. Otherwise, gross and microscopic examination of the brain was unremarkable; in particular, no significant changes were found in the motor cortex, basal ganglia, hypothalamus, cerebellum, pontine nuclei, and motor nuclei of cranial nerves III, IV, VI, and XII.

Light microscopically, the spinal cord showed a normal architecture with normal myelination for age. In the corticospinal tracts sudanophilic material (Oil Red O, Sudan Black) and increased HLA-DR expression (monoclonal mouse anti-human, clone HCR3/43, isotype IgG1, kappa; Dako, Glostrup, Denmark) were absent. The Clarke's and intermediolateral columns, the nerve roots, and a small spinal ganglion that was available for microscopic examination were normal. However, compared to an age-matched control the ventral horns of the spinal cord showed mild neuronal loss. Some motor neurons in both the thoracic and lumbar spinal cord showed swelling, eosinophilic and/or vacuolar change, but basophilic inclusions were absent.

Only in the lumbar spinal cord the anterior horns contained dispersed axonal swellings and multiple motor neurons (up to 50%)

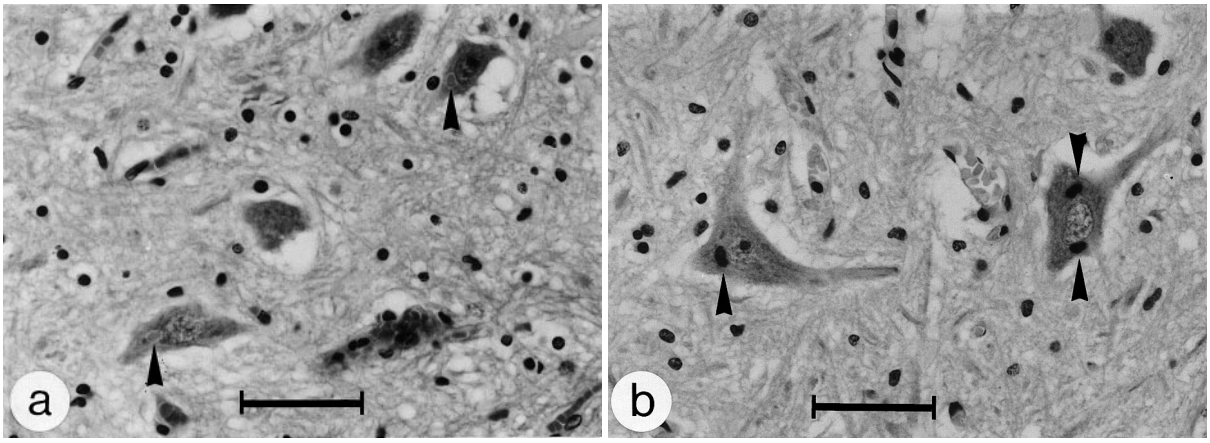

Fig. 1a, b Light microscopy of Bunina bodies (BBs, *arrowheads*) in motor neurons of lumbar spinal cord. **a** Hematoxylin-eosin staining showing minute paranuclear eosinophilic inclusion. **b** Strong anti-human cystatin-C staining of the BBs (hematoxylin counter staining). *Bars* = 50 μm

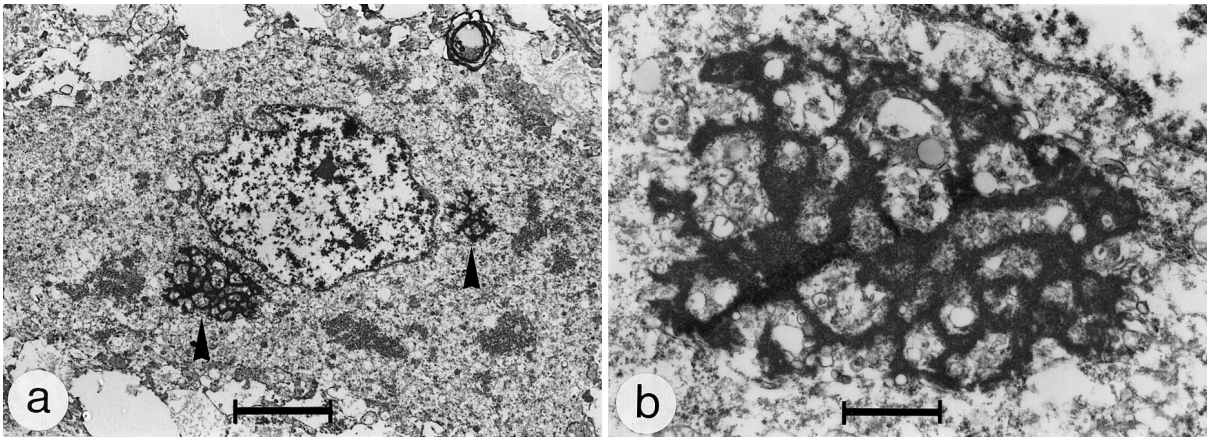

Fig. 2 **a** Transmission electron microscopy of motor neuron in lumbar spinal cord showing two paranuclear Bunina bodies (*arrowheads*) and dispersed Nissl substance in the cytoplasm. **b** Higher magnification of one of the Bunina bodies. *Bars* **a** = 5 μm, **b** = 1 μm

showed one or two discrete, eosinophilic, rounded or more irregular cytoplasmic inclusions, negative with periodic acid-Schiff (PAS) and Bodian staining, with a diameter of 3–8 mm and paranuclear localization (Fig. 1a). Immunohistochemically, the inclusions were strongly human cystatin-C positive (Dako) (Fig. 1b), variably ubiquitin positive (Dako), but tau (Sigma, St. Louis, Mo.) and neurofilament negative. Such cystatin-C-positive inclusions were absent in the rest of the central nervous system. Ultrastructurally, they consisted of anastomosing bands of amorphous or granular, electron-dense material with dispersed membrane-bound vesicular structures in between those bands (Fig. 2a, b). The distribution and the light microscopic, immunohistochemical and ultrastructural features of these intraneuronal inclusions are those of BBs.

Discussion

The MND in this 2-month-old girl is not obviously consistent with any of the known neuromuscular diseases. Involvement of ocular and facial muscles, in combination with the absence of 'floppiness', as observed in our patient, are uncommon in the severe infantile form of SMA, also designated as SMA type I, or Werdnig-Hoffmann's disease [9, 10]. Furthermore, the SMN gene in the region 5q11.2–5q13.3, deleted in more than 95% of patients with SMA type 1 [10, 11], was normal in our patient. Also, the histology of the soleus muscle was clearly neurogenic but different from classical Werdnig-Hoffmann's disease, in which large numbers of atrophic type I or II fibers are accompanied by isolated or grouped hypertrophic type I fibers. We, therefore, consider the diagnosis of the usual variant of SMA type I in our case as unlikely.

BBs, described in sporadic and familial ALS and ALS cases from Guam [4], are considered specific for ALS [3–7]. The staining with anti-human cystatin-C antibodies differentiates BBs from other neuronal inclusions such as cytoplasmic lamellar bodies [5]. The origin of BBs is unclear; they might represent an abnormal accumulation of unknown proteinaceous material associated with the Golgi apparatus [4]. The combination of corticospinal function loss, BBs in lower motor neurons and muscular denervation atrophy is compatible with ALS. However, the presence of autonomic disturbances and the absence of any histological sign of degeneration of the corticospinal tract argue against this diagnosis [8]. On the other hand, autonomic dysfunction is infrequently reported as a life-threatening complication in patients with the major dystrophies and other well-defined neuromuscular disorders [12], including ALS [13]. Since dysautonomia was responsible for the death in our patient, death might possibly have occurred too early in the course of the disease for morphological changes in the corticospinal tracts to become manifest.

Very few juvenile ALS cases (onset of symptoms between 10 and 20 years of age) have been described. Some of these were accompanied by basophilic instead of eosinophilic inclusions in motor neurons (see references cited in [13, 14]). Two reports were found in the literature on infants that were suggested to suffer from ALS [1, 2]. These patients were also spastic rather than hypotonic. The patient reported by Norman and Kay [1] was originally reported to suffer from an atypical variant of SMA, but Lee et al. [2] later suggested a diagnosis of infantile ALS [2]. In contrast to our case, these patients had no inclusions in the lower motor neurons.

In conclusion, the presentation of the child reported here with MND, autonomic dysfunction and BBs is uncommon for the usual forms of MND, i.e., SMA and ALS. Similar cases were not found in the literature. After extended examination two diagnostic possibilities remain: (1) an as-yet-undescribed MND, possibly in the past considered as (a variant of) SMA type I, with autonomic disturbances and BBs; this possibility implies that BBs are not specific for ALS, and (2) an infantile form of ALS with a fulminant course and early death. If this were true, it would be the first infant described with ALS.

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