The morphological studies of muscle biopsy specimens have shown normal or non-specific changes in the reported cases. We studied immunohistochemical localisation of myoglobin in biopsied muscles. Myoglobin, a small molecule (17,000 daltons), is a soluble protein and is found abundantly in cardiac and skeletal muscles. Serum myoglobin increase with muscle cell damage, and it is a more sensitive indicator than CK activity. Sidney et al. have shown using an indirect immunofluorescent technique that myoglobin disappears from cardiac muscle fibres and appears only in the interstitial spaces after 30 minutes of ligation of a coronary artery. Interestingly, immunohistochemical study of our case revealed that some muscle fibres, mainly small atrophic fibres, were negative for myoglobin stain in contrast with positive stain of the remaining fibres. This suggests that hypocalcaemia may lead to myoglobin leakage from skeletal muscles. With respect to the experimental data of Streffer et al., who demonstrated the leakage of cellular enzymes in calcium-free media, Kruse et al. suggested that hypocalcaemia may lead to reversible alterations in enzyme contents of skeletal muscles without structural changes. Finally, our findings indicate that hypocalcaemic myopathy is a distinct clinical entity.

HARUYASU YAMAGUCHI
KOICHI OKAMOTO
MIKO SHOII
MITSUNORI MORIMATSU
SHUNSAKU HIRAI
Department of Neurology,
Gunma University School of Medicine,
Showamachi, Maebashi, Gunma,
371 Japan

References


Diagnosis of juvenile-adult form of neuroaxonal dystrophy by electron microscopy of rectum and skin biopsy

Sir: Generalised neuroaxonal dystrophy (NAD) was originally described as the pathological hallmark of an infantile neurologic disorder which is characterised by delayed motor and speech development and combinations of dystonia, hypotonia or rigidity and spasticity, optic nerve involvement, and dementia. The disease is often familial. It terminates fatally toward the end of the first decade of life. It became obvious that late-onset forms of neuroaxonal dystrophy exist, which begin in late childhood or adolescence and present with a more or less protracted course. Whether these diseases are truly different nosologic entities from the disorder first described by Hallervorden and Spatz in 1922 and bearing their names, is still a matter of debate. By neuropathological definition, Hallervorden-Spatz-syndrome is a localised form of neuroaxonal dystrophy with predilection of the disease process for the pallidum and substantia nigra, in which pathological pigmentation is accumulated. Though abnormal pigmentation is a pathognomonic feature of Hallervorden-Spatz-syndrome, it has occasionally been observed also in other infantile forms of generalised neuroaxonal dystrophy.

If the diagnosis is suspected during life, it should be ascertained by biopsy. In infantile and late-infantile forms of neuroaxonal dystrophy, brain biopsy, may be replaced by biopsy of tissue other than CNS including peripheral nerve and motor end plates, rectum, skin and conjunctiva and dental pulp. Much less information is available about late-onset cases. A cortical brain biopsy established the diagnosis in a sporadic case of a young adult with neuroaxonal dystrophy. We report on a patient with juvenile-adult neuroaxonal dystrophy, in whom electron microscopy of rectal and skin biopsies verified the diagnosis.

A 32 year old Caucasian woman had an unremarkable family history. She first developed signs of the disease at age 14 years, when she began to articulate poorly. At that time her school performance was still high, but deteriorated, so that she graduated from high school with low marks. She did well in gymnastics and was reported to be "clumsy". At 23, her handwriting became poor, and first dystonic and athetoid postures were observed. She was examined in this medical centre at age 31. Previous efforts had failed to provide a diagnosis. Her physical examination was normal. On neurological examination she had a severe dystonic and athetoid gait disorder but was still able to walk unaided. Her speech was barely intelligible due to disturbed articulation and prosody. Athetoid movements were absent at rest and when she was not tense but with effort, her fingers especially of the right hand remained in a dystonic posture. Examination of the cranial nerves revealed abolished vertical and slowed horizontal optokinetic responses. Muscle stretch reflexes were normoactive on both sides. Both plantar responses were flexor. Muscle tone of the limbs was slightly decreased. Sensation was undisturbed. There were no obvious cerebellar signs.

On psychological testing, memory impairment and dull affect were observed. Her performance IQ of 96 compared with the premorbid IQ of 136. There were signs of an organic syndrome on Benton visual retention and Raven SPM tests. Electroencephalography was normal. Computed tomography and magnetic resonance imaging showed a widening of the third ventricle at the upper limit of normal but were otherwise unremarkable. There were no signs of peripheral nerve involvement as determined by electrodiagnosis and EMG. Visual and auditory evoked potentials were normal. Delayed latencies, and somatosensory evoked potentials a slight reduction in amplitude of the early component.
Repeated complete blood counts, blood chemistries, urinalyses, and CSF examinations were inconclusive. Vitamin levels were determined because of possible vitamin E deficiency. No abnormalities were found. The alpha-tocopherol level was 1.71 mg/dl (normal 0.5-2 mg/dl). Serum ceruloplasmin levels ranged between 22.4 and 26.9 mg/dl (normal 15-60 mg/dl).

On neurologic examination 6 months and 1 year later, that is, at age 32, her neurologic status had clearly further deteriorated. Particularly the athetoid and dystonic movement disorder and the gait had worsened. CT scan, MRI and electrodiagnosis had not significantly changed. Skin and rectum biopsies were performed at age 31 and are described below.

Tissue from the rectal wall and skin was fixed immediately with phosphate-buffered 2.5% glutaraldehyde solution (pH 7.4), dehydrated, and embedded in epoxy resin. One μm-thick sections were stained with toluidine blue and served to locate intramural plexuses of the rectum and cutaneous nerves. Specific areas were examined further on ultrathin sections with a Hitachi 600 electron microscope.

In the rectal biopsy section, toluidine blue-stained sections 1 μm-thick revealed a few intramural nerve cells and nerve fibres. Beneath the mucosal surface and adjacent to the mucosal crypts, individual nerve fibres displayed spheroid enlargements suggesting dystrophic terminals. On electron microscopy these spheroids reached diameters up to 20 μm. They were crowded with multilamellar, multivesicular, and granular bodies (fig 1a, b). Some of the larger spheroids (probably depending on the section plane), contained a central conglomerate of tubulo-vesicular structures (fig 1c). They were embedded in an amorphous material and were sometimes surrounded by the same substance. The spheroids were covered by thin Schwann cell processes. Small spheroids or merely somewhat swollen axons were also present. They contained accumulated vesicles and mitochondria some of which had degenerated and displaced the normal axonal constituents. They may represent early stages of the neuroaxonal dystrophy process or axons sectioned near a terminal spheroid. Toluidine blue-stained sections of the skin allowed the tracing of nerve fibres within the dermis. With the electron microscope, some revealed spheroids similar to the ones described above (fig 2). Their average diameter was smaller, however, but the accumulated pathological structures were identical.

Dystrophic swelling of axons leading to spheroids may occur in several different
pathological conditions. In the CNS of humans and other mammals this lesion has some predilection for certain anatomical sites in advancing age, 23, 24 vitamin E deficiency (for example cystic fibrosis, congenital biliary atresia 25 or after experimental deficiency 26, 27), and secondary to toxic influences such as antineoplastic chemotherapy. 28 Generally the conditions described can be ruled out as a cause for axonal dystrophic swelling when primary neuroaxonal dystrophy is considered, as in our case. Clinical criteria also differentiate several unrelated systemic diseases in which axonal spheroids occur such as kinky hair disease, 29 ataxia telangiectasia, 30 or Canavan's disease. 31 Our experience with rectal biopsies in lipidoses includes only one case with comparable spheroids of intramural axons in a patient who had Niemann-Pick disease Crocker type C (unpublished). Even in this case, the axonal spheroids could be distinguished by electron microscopy from the swellings seen in our patient. In Niemann-Pick disease type C they contain multilamellar and complex cytoplasmic bodies, 32 but lack the tubulo-vesicular conglomerates in the spheroid centres. In our case, axonal spheroids were characteristic of neuroaxonal dystrophy. Comparable electron microscopic findings were reported from brains of late-onset cases after necropsy, 23 33 and from a young adult patient in whom a cortical biopsy was performed. 22 The peripheral biopsy specimens in infantile cases, particularly of rectum 17 18 and skin, 20 were quite similar. Our patient may be classified under the late-onset neuroaxonal dystrophy forms which have an unusually protracted course. 22 23 25 It is not known whether our patient has pigmented dystrophy of the pallidum.

Although we do not know whether in cases of strictly defined Hallervorden-Spatz-syndrome, electron microscopic examination of rectum and skin biopsies is equally rewarding, our observations suggest that peripheral biopsy sites should be chosen before brain biopsy is considered.

We sincerely thank Prof A. Koeppen for critical comments and Brigitte Rohbeck for critical technical help.

References
32 Vuia O. Neuroaxonal dystrophy, a juvenile-
Letters

Stridor during dystonic phases of Parkinson's disease

Sir: Stridor is very rare in both idiopathic Parkinson's disease and in Parkinsonism after encephalitis lethargica and contrasts with the Shy-Drager syndrome in which it regularly occurs due to selective paralysis of abduction of the vocal cords. We describe, in two patients with longstanding idiopathic and levodopa responsive Parkinson's disease, severe attacks of stridor during phases when they were dystonic elsewhere.

In March 1986, a 66 year old man was referred by his physician because of episodic breathing difficulties. In 1978 he had developed a left sided resting tremor. There was a satisfactory response to levodopa/carbidopa and benzhexol. Two years later while on Sinemet 275, two tablets daily and benzhexol 2 mg bd, he reported painful curling up of the toes of his left foot soon after awakening. These episodes persisted despite an increase of levodopa to Sinemet 275, three tablets daily. By 1984 he noted that in addition to dystonic posturing of his left foot, he simultaneously found difficulty with breathing, particularly inspiration. Shifting the evening dose of Sinemet from 1800 to 2200 hours resulted in a reduction in the incidence of this problem, but dystonia tended to recur at the time the next dose of Sinemet was due. By taking Sinemet 275 half a tablet every 2 hours, dystonic episodes were avoided.

In order to better understand the nature of his breathing problems we arranged to observe one of his dystonic episodes after the omission of Sinemet. As benzhexol was then four hours after his last dose of Sinemet. The attack began with sustained inversion and plantar flexion of the left foot with flexion of the toes. A few minutes later he developed mild retroscoliosis and became apprehensive. His breathing became laboured with the development of stridor. He made loud gagging noises and repeatedly raised his hands to his throat as if being strangled. He was unable to speak. Sustained dystonic contractions of all the facial muscles including platysma were seen. He slumped down his armchair into a most unguainly posture so that the back of his head rested on the back of the chair. He said afterwards that he usually lay supine during an attack, presumably because the retroscoliosis is somewhat relieved. His distressing ordeal was ended when he took another full tablet of Sinemet 275 with rapid improvement in stridor, although dystonic posturing of the left foot persisted for over an hour.

Careful examination of his vocal cords showed no abnormality though it was not possible to examine them during the attack.

Parkinson's disease was diagnosed in the second patient at the age of 45 years following the development of clumsiness and slowness of movement of the left arm and leg. He became asymptomatic on levodopa until age 54 when peak dose choreiform dyskinesia was noted. Orphenadrine had been added to his treatment regime earlier. A year later he developed visual hallucinations and Sinemet 110 was reduced from three to two tablets daily. Three days later he developed intermittent breathing difficulties, stridor and dysphonia with dystonic retraction of the jaw, wide gaping of the mouth with facial grimacing. The episodes were particularly distressing to the patient and his wife at night. On admission to hospital mechanical obstruction to the airway was considered, but urgent indirect laryngoscopy was normal showing a full range of movement of the vocal cords. It was observed, however, that by forcibly pulling the jaw forward the stridor could be relieved. The dystonia was thought to be due to an under dosage of levodopa so Sinemet 110 was increased to four tablets daily. After two days the episodes of dystonic stridor ceased. A month later his Sinemet dose had to be decreased owing to the recurrence of confusion and hallucinations. Two months later, there was a further emergency admission for respiratory distress and stridor. The dystonic features were similar but more severe than during previous admissions. The patient was semi-conscious, restless and unco-operative and an anaesthetist considered that the obstruction to the airway was so critical that urgent tracheostomy was required. A mini-tracheostomy tube was inserted and he rapidly became more settled. The tube was left in situ for seven days while his Sinemet regime was increased to half a tablet six times daily. There has been no recurrence of stridor during three months follow-up on this regime.

The mechanism of stridor in these two cases seemed to differ from the laryngeal spasm previously described in Parkinson's disease in that the main obstruction to airflow occurred above the level of the larynx. The vocal cords were not adducted in either patient, thus it seems likely that dystonia of the pharyngeal, jaw and neck muscles played a significant part. Breathing difficulties of this sort have been described rarely in the late stages of dystonia muscularorum deformans, and in adults with oro-mandibular dystonia who developed neck involvement.

Dystonic responses to levodopa therapy are well recognised in Parkinson's disease, and various patterns have been described. The lack of previous descriptions of dystonic stridor in Parkinson's disease is surprising but it may be a terminal event and hence overlooked as a complete neurological assessment at this stage is rare. Secondly, patients may be living longer because of the support of levodopa allowing new clinical phenomena related to its use to be observed. The dystonia in both our patients responded to higher doses of levodopa and therefore appears to be an under dosage phenomenon.

The spectrum of clinical phenomena classified as dystonic has widened in recent years; for example, spasmodyc dystonia is now recognised as being a form of focal dystonia of the laryngeal muscles. Whether some instances of stridor, currently classified as hysterical, come to be recognised as a form of segmental dystonia remains to be seen.

References


DOC CORBIN

AC WILLIAMS

Department of Neurology,
Queen Elizabeth Hospital,
Edgbaston,
Birmingham, B15 2TH, UK.