Clinical onset and MRI features of Krabbe's disease in adolescence

Although Krabbe's disease typically presents in infancy, onset later in childhood has been described. In both circumstances there is diffuse demyelination, with globoid cells, particularly affecting the centrum semiovale and periventricular areas. However, the infantile form ends fatally within two to five years with progressive psychomotor regression, visual loss, spasticity and myoclonus, whereas older patients generally have a more benign course. In addition, they often have no demyelinating neuropathy or elevation of the CSF protein. Such milder features may result from less severe enzyme defects in the late-onset cases. In keeping with this idea, we report a patient in whom the disease had an exceptionally late onset and benign clinical course, and in whom there was only a partial deficiency of leucocyte galactocerebroside.

The patient, a 37 year old Indian man, developed normally until the age of 13 years, when he noted weakness of his left arm and leg over a few months which affected sporting activities. The weakness then progressed very slowly, with more accelerated deterioration at the age of 26 and 29, after which his right leg was also affected and he developed a tremor of his left arm. There was no disturbance of sphincter function, vision, sensation or intellect. He had a mixed diet and took no medications, and there was no family history of consanguinity or neurological disease.

General examination was unremarkable, with no cutaneous lesions or buccal pigmentation and a stable blood pressure of 130/70 mm Hg. The mental state and vision, including colour perception and fundoscopy, were also normal. There was first degree nystagmus on upgaze, but the cranial nerves and jaw jerk were otherwise normal. The gait was spastic and there was also spastic weakness of the left arm and both legs, which was worse on the left. Moderate cerebellar ataxia of the left arm was noted, the tendon jerks were pathologically brisk, more so on the left, and both plantar responses were extensor. The abdominal reflexes were preserved and sensation was intact.

The blood count and film, erythrocyte sedimentation rate (5 mm/hr), routine bio-chemical tests, endocrine investigations including urinary and plasma cortisols, and assays for very long chain fatty acids were all normal. However, the screen for plasma and leucocyte enzymes revealed a markedly reduced level of galactocerebroside of 0.06 nmol/mg protein/hr (controls 0.22–3.8 nmol/mg protein/hr).

Nerve conduction studies and evoked potentials (visual, auditory and somatosensory) were normal. Lumber puncture was traumatic, the CSF containing 2020 red cells/mm³, 7 white cells/mm³, protein 0.75 g/l and glucose 3.8 mmol/l. CSF electrophoresis did not show IgG oligoclonal bands. A skull radiograph had suggested basilar invagination, which was thought to be the cause of his neurological condition. However, CT with intrathecal water soluble contrast medium from C2 to the posterior fossa showed no compression of the neuraxis, and this was confirmed with MRI. The latter, however, demonstrated bilateral, confluent white matter lesions posteriorly in the peritrigonal and higher parietal regions and in the posterior corpus callosum (figure), without clear abnormalities of the brainstem.

Given the demonstration of white matter disease by the MRI study and the marked deficiency of leucocyte galactocerebroside, it is most likely that the patient had Krabbe's disease. The clinical features of a relatively rapid onset with a hemiparesis, and subsequent slow progression with phases of accelerated disability, have also been noted in previous cases in childhood. As regards alternative diagnoses, there was no evidence for a compressive lesion; the suggestion of basilar invagination on the plain skull radiograph was not confirmed, indicating the need to investigate symptomatic cases further if compression of the neuraxis is suspected. Multiple sclerosis was also improbable given the results of imaging, evoked potentials and CSF examination. Finally, both adrenoleucodystrophy and alternative leucocyte enzyme defects could be excluded by normal cortisol levels and assays for very long chain fatty acids and for other leucocyte enzymes. However, the posterior cerebral distribution of white matter lesions in our case was not typical of Krabbe's disease, where diffuse lesions of the centrum semiovale, periventricular white matter and hemispheric deep grey matter have been reported. Recently, posterior lesions have been described in a childhood case of Krabbe's disease using CT, although such appearances have previously been regarded as characteristic of adrenoleucodystrophy.

Finally, it is notable that the residual enzyme level in our case would be considered high for infantile Krabbe's disease, where activities are typically less than 5% of control values. However, the biochemical changes are relatively mild in older cases. In describing higher residual enzyme activities and maximum velocities of the enzyme reaction in childhood cases of Krabbe's disease, Farrell and Swedberg suggested that different allelic mutations of the galactocerebroside gene could cause different clinical forms of the disease. Subsequently, levels of partial deficiency similar to the present one have been found in cases with onset in childhood. Since these levels are intermediate between those occurring in infantile cases and in heterozygotes, who are apparently unaffected clinically, the threshold, minimum reduction of galactocerebroside activity associated with infantile cases, has not been reached.
with a neurological disorder therefore remains to be defined.

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Mononeuropathies in thyrotoxicosis

Recently Iguchi et al.1 reported two thyrotoxic patients with associated mononeuropathies and suggested a causal relationship. Other authors, such as, Beard et al.2 described the association between carpal tunnel syndrome (CTS) and Graves’ disease. Also Siegler and Rearters3 observed a bilateral peroneal palsy in a patient with thyrotoxicosis. Despite these observations the prevalence of neuropathies in thyrotoxicosis is unknown.

In a prospective study on 150 patients with CTS we found two patients with past history of thyrotoxicosis.3 This fact induced us to initiate a prospective study, presented in preliminary form at the XLI annual meeting of the Spanish Society of Neurology,4 to determine the frequency and course of CTS in thyrotoxic patients.

Sixty untreated thyrotoxic patients were studied clinically and by electromyography (ENG): in 11, clinical symptoms of CTS were present (nocturnal paraesthesia or other symptoms that suggested median nerve damage). In eight of these 11 patients, ENG supported the clinical diagnosis (ENG diagnosis of CTS was accepted when sensory NCV across carpal tunnel was less than 45 m/s). Three patients had the simultaneous onset of symptoms of CTS and thyrotoxicosis. All patients were followed clinically and by ENG for two years. The evolution of CTS and thyrotoxicosis was analogous and after two years all patients were free of symptoms. However, in one of them, with uncontrolled thyrotoxicosis, ENG studies deteriorated. The other patients, with remission of thyrotoxicosis, had normal ENG values in one year. Meanwhile in the other the ENG was unchanged. In another five patients of the series we also found ENG abnormalities supporting a subclinical CTS.

The course of these cases was also parallel to clinical thyrotoxicosis. Another patient with thyrotoxicosis developed a right peroneal palsy due to nerve compression at the head of the fibula favoured, by the fiercely muscular atrophy. After six months the recovery was complete.

Our results suggested that 5% of thyrotoxic patients developed a CTS as a consequence of thyrotoxicosis. In these cases we observed a good CTS evolution, always parallel to thyroid status. Excess thyroxine might play a role in the development of CTS. Other factors such as loss of weight, weakness, infiltration of the nerve with mucopolysaccharides and infiltrative dermopathy4 can also contribute to generation of mononeuropathies in thyrotoxic patients.  

References

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Mental representation and temporary recovery from unilateral neglect after vestibular stimulation

Vestibular stimulation temporarily reduces unilateral visual neglect.5 Cappa et al.6 observed improvement of personal neglect and anosognosia for hemiplegia after vestibular stimulation. The effects on anosognosia and personal neglect suggest an influence of vestibular stimulation not only on the cerebral mechanism of attention to external stimuli, but also on deep cerebral structures involved in the mental representation of space.7 Our study aimed to assess the effect of vestibular stimulation on mental visuospatial representation in subjects with unilateral neglect.

Five right handed subjects with clinical and CT evidence of right hemisphere damage (four ischaemic stroke and one spontaneous intracranial hemorrhage) were included, one month of onset of illness. They all presented signs of left spatial neglect as revealed by a modified version of the Albert’s line-crossing test.8 In this test the subject had to count out 21 lines, drawn in an apparently random manner on a sheet of paper, one line in the centre and 10 on each half of the paper. Personal neglect and anosognosia for motor deficits were evaluated by a four point rating scale.9 A visual representation task was carried out in the absence of stimuli from personal or extrapersonal space. The subject was asked to describe the cathedral square of Milan (Piazza del Duomo) from two opposing viewpoints; the results were evaluated by counting the number of landmarks unequivocally identified as belonging to the left and right sides of the piazza respectively, compared to the patients’ (imagined) viewpoint. The battery of tests, taking less than 10 minutes, was applied immediately before vestibular stimulation (baseline assessment). Vestibular stimulation was induced by a temporary displacement of the left external auditory canal with approximately 30 cc of ice cold water. When a clinical reaction was manifest (nystagmus towards the right or possibly tonic displacement of the head or gaze to the left) the battery was repeated. The results are given in the table.

Table Neuropsychological assessment before and after vestibular stimulation

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<td>Line-crossing test*</td>
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<td></td>
<td>after (L→R)</td>
<td>3</td>
<td>2-3</td>
<td>4-5</td>
<td>3-7</td>
</tr>
</tbody>
</table>

*Number of recorded lines on left side (max 10).
†Four-point scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe (for details see ref. 5).
‡Number of landmarks on left (L) and right (R) side.

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