Delayed Diagnosis

Adult metachromatic leukodystrophy with an unusual relapsing – remitting course

Menachem Sadeh¹, Arie Kuritzky², Eitan Ben-David³ and Yochanan Goldhammer¹

Departments of¹Neurology, The Chaim Sheba Medical Center, Tel Hashomer, ²Neurology and ³Pathology, Beilinson Medical Center, Petach Tikva, and Sackler School of Medicine, Tel Aviv University, Israel

Summary: A 46 year old woman had a relapsing–remitting course of hemiparesis, disorientation, paraparesis and seizures, followed by progressive dementia, spasticity and ataxia. Computed tomography at onset showed a parietotemporal hypodense area with diffuse mottled enhancement obliterating the lateral ventricle. Subsequent scans demonstrated symmetric periventricular non-enhancing hypodensities, progressive ventricular enlargement and atrophy. Adult metachromatic leukodystrophy was diagnosed on the basis of low leukocyte arylsulphatase A level and metachromatic material accumulation at neural nerve biopsy.

Introduction

Adult metachromatic leukodystrophy (MLD) presents with personality changes, emotional lability, schizophrenic-like disorder, memory and thinking deterioration and reduced visual–spatial discrimination.^{1,2} The course is slowly progressive lasting several years or even decades^{2–5} leading to severe dementia, spastic quadriparesis, blindness and mutism. We wish to report a case of adult MLD presenting in an unusual course as a chronic relapsing encephalomyelopathy.

Case report

A 46 year old woman was admitted to the department of neurology for the evaluation of a febrile illness with mental changes, dizziness and vomiting of 8 days duration. The past history was unremarkable and no family member had neurological or psychiatric disorders. Her temperature was 37.8°C and there was mild nuchal rigidity. She was well oriented but short-term and intermediate memory were disturbed and calculation and abstraction

capacities markedly reduced. Several days later she developed a right hemiparesis. Cerebrospinal fluid (CSF) pressure was 200 mm of water with 15 lymphocytes per mm³ and normal chemical analysis, culture was negative and herpes antibody titre not significantly raised. Electroencephalogram (EEG) showed left temporal slow wave activity. Computed tomography (CT) demonstrated wide diffuse hypodense areas in the left frontal and temporal lobes with mottled enhancement after contrast medium injection (Figure 1a–c). Left carotid angiography showed a mild left to right midline shift and irregular tortuous delicate arteries in the temporal lobe. She was diagnosed as having meningoencephalitis, and treated with steroids. After an acute psychotic reaction these were replaced by antipsychotic agents. Phenytoin was added because of grand mal seizures. She recovered over several weeks with abnormal neurological findings and only slight parietotemporal hypodense areas with no mass effect and symmetric ventricles on repeated CT (Figure 1d).

A week later severe proximal weakness of the lower limbs with difficulty in walking developed rapidly. Severe weakness of the iliopsoas muscles, moderate weakness of the glutei and mild distal weakness were noted but upper limb strength was normal. Deep tendon reflexes were more active on the right side and plantar responses were flexor. There was loss of position sense in the lower

Correspondence: M. Sadeh, M.D., Department of Neurology, The Chaim Sheba Medical Center, Tel Hashomer 52621, Israel.

Accepted: 30 July 1991

Figure 1 CT scans at various stages of the disease. **a–c**, Contrast enhanced CT at onset showing bilateral white matter hypodensities, much more pronounced on the left side, with small areas of enhancement. **d**, After recovery from the acute episode only a small left hypodense area remained. **e–g**, Following CT scans demonstrate bilateral periventricular hypodense areas. **h,i**, Marked cortical atrophy and ventricular enlargement are apparent.

extremities. She was disoriented, apathetic with defective memory. Laboratory studies including creatine kinase level were normal. EEG showed bilateral diffuse slow (3–4 s) wave activity. CSF analysis yielded 20 lymphocytes per mm³, 375 mg/dl protein and normal glucose level. Oligoclonal IgG was not present. CT demonstrated bilateral frontal and left parietal white matter hypodensities (Figure 1e,f). Common peroneal and posterior tibial nerve conduction velocities were 40–48 m/s. Occasional fibrillations/fasciculations were seen on electromyography of lower limbs. On treatment with 60 mg prednisone daily there was gradual improvement of strength and mental status. She became oriented, was able to walk on a wide base with almost normal strength in all muscles, however, a mild cognitive impairment remained. Repeated EEG, CSF analysis and brain CT were unchanged.

After six months of relatively good functioning at home, she developed acute severe weakness of the right upper limb and mild proximal weakness of the lower. Tendon reflexes were hyperactive on the right with exterior plantar response. Results of EEG, lumbar puncture and CT of brain were similar to those on previous admissions. Weakness improved within 2 weeks but her mental status gradually deteriorated, ataxia, dysarthria and mild spasticity of lower limbs persisted. CT showed diffuse symmetric ventricular enlargement with periventricular hypodensities (Figure 1g). There was a mild diffuse slowing of nerve conduction velocity. Sural nerve biopsy examined by light microscope showed accumulation of metachromatic granules in Schwann cells, in macrophages and between nerve fibres, as well as demyelination and mild axonal loss. Electron microscopy revealed multiple inclusion bodies in Schwann cell cytoplasm, and axonal demyelination (Figure 2). Arylsulphatase A in leukocytes was 18.7 nmol/mg protein/h (normal 73–199 nmol/mg protein/h).

A further gradual deterioration followed with increased dementia, spasticity, ataxia and epileptic seizures. CT showed cortical atrophy and marked ventricular enlargement (Figure 1h,i).

Discussion

The unusual course of this patient's disease led to a 2 year delay in making the diagnosis. Metachromatic leukodystrophy was suspected only when progressive dementia developed accompanied by diffuse nerve conduction slowing; the diagnosis was then established by low leukocyte arylsulphatase A levels and the presence of metachromatic deposits in sural nerve biopsy. All previous case reports have noted a pattern of intellectual deterioration

Figure 2 This electron micrograph shows a demyelinated axon (Ax) and inclusion material within an adjacent Schwann cell ($\times 20,000$).

and behavioural changes progressing rapidly over several years in some patients and in others slowly over decades,^{2–5} but none, to the best of our knowledge, manifesting with relapsing and remitting focal and generalized neurological signs.

CT findings in MLD are bilateral symmetric non-enhancing frontal and parietal hypodensities and ventricular enlargement.^{6–9} In contrast, our patient's CT at onset showed asymmetric hypodense areas with mottled enhancement and obliteration of the lateral ventricle (Figure 1a–c), suggesting a mass effect. Such changes, not described previously, correlate with the acute onset and asymmetric clinical signs. Only at later stages did the CT show bilateral symmetric hypodense periventricular areas, gradual ventricular enlargement and cortical atrophy. These findings are in accordance with previous observations of sequential scans suggesting 3 stages of CT features: normal, white matter hypodensities and finally atrophy.¹⁰

CSF analysis in previously reported cases was normal except for mildly elevated protein values.² Several lumbar taps in our patient yielded mild pleocytosis and occasionally increased protein levels, compatible with an inflammatory response at the acute onset and during the relapsing course. This concept is further strengthened by the clinical improvement after steroid therapy. However, the pathogenesis of acute exacerbations is obscure.

We suggest that adult MLD should be included in the differential diagnosis of white matter abnor-

malities in CT, even if they are asymmetric, enhancing or appear to have mass effect. With the advent of magnetic resonance imaging (MRI), white matter abnormalities may be diagnosed earlier and probably more specifically, than by CT. In 2

patients reported with adult MLD, MRI showed widespread periventricular high intensity T2 signals, more diffuse than those observed by CT.^{8,9} Unfortunately MRI was not available for this patient.

References

1. Manowitz, P., Kling, A. & Kohn, H. Clinical course of adult metachromatic leukodystrophy presenting as schizophrenia. *J Nerv Mental Dis* 1978, **166**: 500–506.
2. Bosch, E.P. & Hart, M.N. Late adult-onset metachromatic leukodystrophy in a 63 year old man. *Arch Neurol* 1978, **35**: 475–477.
3. Hoes, M.J.A., Lamers, K.J., Hommes, O.R. & ter Haar, B. Adult metachromatic leukodystrophy: arylsulfate A values in four generations of one family and some reflections about the genetics. *Clin Neurol Neurosurg* 1978, **80**: 174–188.
4. Tagliavini, F., Pietrini, V., Pillery, G. *et al.* Case report. Adult metachromatic leukodystrophy: clinicopathological report of two familial cases with slow course. *Neuropath Appl Neurobiol* 1979, **5**: 233–243.
5. Austin, J., Armstrong, D., Fouch, S. *et al.* Metachromatic leukodystrophy (MLD). VIII. MLD in adults: diagnosis and pathogenesis. *Arch Neurol* 1968, **18**: 225–240.
6. Skomer, C., Stears, J. & Austin, J. Metachromatic leukodystrophy (MLD) XV. Adult MLD with focal lesions by computed tomography. *Arch Neurol* 1983, **40**: 354–355.
7. Finelli, P.F. Metachromatic leukodystrophy manifesting as a schizophrenic disorder: computed tomographic correlation. *Ann Neurol* 1985, **18**: 94–95.
8. Waltz, G., Harik, S.I. & Kaufman, B. Adult metachromatic leukodystrophy. Value of computed tomographic scanning and magnetic resonance imaging of the brain. *Arch Neurol* 1987, **44**: 225–227.
9. Reider-Grosswasser, I. & Bornstein, N. CT and MRI in late-onset metachromatic leukodystrophy. *Acta Neurol Scand* 1987, **75**: 64–69.
10. Barnes, D.M. & Enzmann, D.R. The evolution of white matter disease as seen on computed tomography. *Radiology* 1981, **139**: 378–383.