Reminder of important clinical lesson

Diffusion and ADC-map images detect ongoing demyelination on subcortical white matter in an adult metachromatic leukodystrophy patient with autoimmune Hashimoto thyroiditis

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Summary

Adult-onset metachromatic leukodystrophy (MLD) often shows schizophrenia- or encephalopathy-like symptoms at an early stage, such as behavioural abnormalities, cognitive impairment, mood disorders and hallucinations. The authors report the case of an adult woman with MLD who had been given antipsychotic medication for schizophrenia. In the differential diagnosis, screening of auto-antibodies was important for ruling out other encephalopathies as she had a euthyroid Hashimoto thyroiditis. Diagnosis was based the results of MRI, nerve conduction velocity, sensory evoked potential, motor evoked potential, lysosomal enzyme activity and gene analysis studies. Brain MRI showed diffuse demyelination spreading from the deep white matter to subcortical area as high signals at the edges of these lesions in diffusion and apparent diffusion coefficient-map images with the U-fibres conserved. The authors diagnosed adult-onset MLD coexisting with euthyroid autoimmune Hashimoto thyroiditis.

BACKGROUND

Metachromatic leukodystrophy (MLD) is an autosomal recessive lysosomal storage disease with an estimated incidence of 1:40 000, characterised by demyelination of the white matter in the central nervous system and the peripheral nerves with sulfatide accumulations. Arylsulfatase A (ARSA) deficiency with its gene mutations is the main cause of MLD. ARSA hydrolyses various sulfatides, including the major sulphate-containing lipids of the nervous system. MLD impairs the growth or development of the myelin sheaths, the fatty covering that acts as an insulator around nerve fibres. Screening assay of ARSA activity followed by sequencing of ARSA gene mutations is helpful to confirm a diagnosis of MLD. The adult form of MLD has sometimes been misdiagnosed as schizophrenia and treated with antipsychotic medication because of behavioural abnormalities, cognitive impairment, mood disorders and hallucinations.¹ MRI at the time of diagnosis often shows symmetric white matter involvement sparing the arcuate (U-) fibres.

Hashimoto encephalopathy is also a rare disease with schizophrenia-like symptoms and often progressive cognitive impairment, and can characteristically be treated with corticosteroids.² Although patients usually show euthyroid function, some serum autoantibodies related to chronic thyroiditis have been detected. Autoantibodies against the amino (NH₂)-terminal of α -enolase (NAE) were reported to be a marker with a high prevalence and high specificity to this encephalopathy.³ MRI showed various areas of cerebral cortex, especially the temporal lobes, with involved deep white matter.⁴

Here the authors report an adult case of MLD with detectable autoimmune antibodies related to chronic

thyroiditis suspected to be complicated by Hashimoto disease but not encephalitis.

CASE PRESENTATION

A 25-year-old woman presented with mental deterioration and progressive aphasia over the preceding 4 years. At age 23, she often lost her way home. At age 24, she complained of visual hallucinations and had incontinence of faeces. She had been treated with antipsychotic medication for schizophrenia-like symptoms by a psychiatrist for 2 years before presenting at our hospital. Her mother and maternal grandfather have chronic thyroiditis; there is no intermarriage among relatives. Physical examination revealed mild thyroid gland swelling but otherwise normal physical findings. Neurological examination revealed decreased intellectual function: her Mini-Mental State Examination score was 7/30, and the revised form of the Wechsler Adult Intelligence Scale showed a verbal intelligent quotient (IQ) <45, performance IQ <45 and IQ <40. Examination of her optic fundi was normal, which is unusual in lysosomal storage diseases. Her lower extremities showed mild spasticity and pes cavus. Deep tendon reflexes were downgoing at the patella and normal at the Achilles tendon, and plantar reflexes were bilaterally positive, indicating primary and secondary motor neuron involvement. The patient did not complain of sensory disturbance, dysaesthesia or paraesthesia. She was able to walk with a mild steppage gait.

Laboratory tests revealed some autoimmune antibodies related to chronic thyroiditis: antithyroid peroxidase antibody (anti-TPO-Ab) 0.6 (COI (cut-off index) ≤ 0.3) U/ml, antithyroglobulin antibody (Tg-Ab) 15.1 (COI ≤ 0.3) U/ml, and thyroid hormone and thyroid-stimulating hormone levels within the normal range (table 1). In addition,

Table 1 Results of blood laboratory tests

Haematology
WBC 8100/ μ l (neutrophils 58.0%, lymphocytes 31.2%, monocytes 3.6%, eosinophils 6.2%, basophils 0.7%), haemoglobin 12.8 g/dl, platelets $187 \times 10^3/\mu$ l

Biochemistry
T-pro 7.1 g/dl, Alb 4.1 g/dl, BUN 12.2 mg/dl, Cr 0.40 mg/dl, UA 3.6 mg/dl, T-Bil 1.3 mg/dl, γ -GTP 8 U/l, LDH 165 U/l, AST 12 U/l, ALT 12 U/l, CK 43 U/l, NH3 65 μ g/dl, TG 107 mg/dl, HDL-C53 mg/dl, LDL-C 78 mg/dl, CRP <0.05 mg/dl, LA 12.4 mg/dl, PA 0.92 mg/dl, I/P ratio 13.5, P-Glu 77 mg/dl, HbA1c 4.8%

Electrolyte
Na 139 mEq/l, K 3.5 mEq/l, Cl 105 mEq/l, Mg 2.0 mg/dl, Zn 92 μ g/dl, Fe 118 μ g/dl, Cu 98 μ g/dl

Infection
HBs-Ag (–), HCV-Ab (–), TPLA (–), RPR (–), HTLV-1 (–), measles-Ag 16-fold

Endocrine secretion
TSH 2.87 μ U/ml, FT4 1.28 ng/dl (normal 0.90–1.70 ng/dl), FT3 3.05 pg/ml (normal 2.30–4.00 pg/ml), FSH 2.9 mIU/ml (normal 0.50–5.00 μ U/ml), oestradiol 90.8 mIU/ml (normal 30–200 pg/ml)

Immunology
SS-A/Ro 0.2 U/ml (COI <10), SS-B/La 39.4 (COI <10), anti-TPO-Ab 0.6 U/ml (COI <0.3), Tg-Ab 15.1 U/ml (COI <0.3), TS-Ab 90% (normal <180%), TBG 21 μ g/ml (normal 12–28), ds-DNA4 IU/ml (normal <12), scl-70 17.0 (COI <16), Jo-1 0.9 (COI <9), PR3-ANCA (–) (COI <10), MPO-ANCA (–) (COI <20), sIL2R 345 IU/ml (normal 124–466), CH50 54 ml/dl (normal 31–48), C3c 125.9 mg/dl (normal 65–135), C4 24.8 mg/dl (normal 13–35), serum immunoelectrophoresis: IgG mildly increased

Lysosomal enzyme activity in peripheral WBC
 α -galactosidase 76.1, β -galactosidase 34.0, α -glucosidase 2.1, β -glucosidase 21.5, β -hexosaminidase 1030, β -hexosaminidase A 668, α -mannosidase 153.0, β -mannosidase 82.6, α -fucosidase 56.7, β -glucuronidase 89.5, arylsulfatase A 10.0 (normal 98.3 ± 22.2) (unit: nmol/mg protein/h)

Cerebrospinal fluid
Watery, clear, pressure: 65 mm H₂O, cell counts: 10/ μ l (all mononuclear cells), L-pro 130 mg/dl, Glu 59 mg/dl (serum Glu 77 mg/dl), Na 145 mEq/l, LA 14.1 mg/dl. IgG index 0.63, MBP 31.8 pg/ml, oligoclonal IgG band: negative

Activity of arylsulfatase A was significantly low compared with other lysosomal enzymes.

Alb, albumin; ALT, alanine transaminase; Anti-TPO-Ab, antithyroid peroxidase antibody; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CK, creatine kinase; COI, cut-off index; Cr, creatine; CRP, C reactive protein; ds-DNA, antidouble-stranded DNA antibody; FSH, follicle-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; Glu, glucose; GTP, guanosine 5'-triphosphate; HbA1c, haemoglobin A1c; HBs-Ag, hepatitis B surface antigen; HCV, hepatitis C virus antibody; HCV-Ab, hepatitis C virus antibody; HDL, high-density lipoprotein; HTLV-1, human T cell lymphotropic virus type 1; IgG, immunoglobulin G; LDH, lactate dehydrogenase; L-pro, L-protein; LDL-C, low-density lipoprotein cholesterol; MBP, myelin basic protein; MPO-ANCA, myeloperoxidase antineutrophil cytoplasmic antibody; P-Glu, pyroglutamate; PR3-ANCA, proteinase-3 antineutrophil cytoplasmic antibody; RPR, rapid plasma reagin; sIL2R, soluble interleukin-2 receptor; SS-A, Sjögren's syndrome antigen A; SS-B, Sjögren's syndrome antigen B; TBG, thyroxine binding globulin; T-Bil, total bilirubin; TG, thyroglobulin; Tg-Ab, thyroglobulin autoantibody; T-pro, total protein; TS-Ab, antithyroglobulin antibody; TSH, thyroid stimulating hormone; UA, urinalysis; WBC, white blood cell; LA, lactic acid; PA, Pyruvic acid; TPLA, Tereponema Pallidum Latex immuno assay.

autoantibodies against the amino-terminal of NAE³ (a marker for Hashimoto encephalopathy) were also negative. The cerebrospinal fluid (CSF) protein level was clearly high at 130 mg/dl (normal <60 mg/dl) with a low immunoglobulin G (IgG) index of 0.63, and without detectable levels of myelin basic protein (MBP) or multiple sclerosis specific oligoclonal IgG band patterns. Anti-TPO-Ab, Tg-Ab and anti-NAE antibodies were not tested in CSF.

Ultrasound of the thyroid gland showed a normal internal signal without any tumorous images. Brain MRI showed almost symmetrical volume loss, especially around the cerebral ventricles, and diffuse high signals in white matter on fluid attenuated inversion recovery and T2 weighted images, although the U-fibres were conserved (figure 1). Diffusion weighted images showed high signals at the edges of these lesions. In the apparent diffusion coefficient (ADC)-map images, these lesions also presented high signals, which were considered demyelinating changes spreading from deep white matter to the subcortical area. This was confirmed by magnetic resonance spectroscopies showing the typical decrease in N-acetyl aspartate and increase in choline (data not shown). No evidence of tumours was detected by whole body CT scan or by gastroscopy or colonoscopy. EEG showed diffuse θ -activity.

Nerve conduction studies (table 2) showed approximately half speed motor conduction velocity with almost normal compound muscle action potential voltage on the patient's median, ulnar and peroneal nerves and also undetectable sensory neuron action potential at the ulnar, tibial and sural nerves, suggesting demyelination of both the motor and sensory peripheral nerves. Lack of abnormal temporal dispersion indicated diffuse demyelination rather

than chronic inflammatory demyelinating polyneuropathy or Guillain–Barre syndrome. The sensory evoked potential study of median nerves showed that bilateral N9 peaks were not induced and the interval latency between N13 and N20 peaks was over twice normal. In the motor evoked potential (MEP) study of the right first dorsal muscle and abductor pollicis muscle, MEP latency and central motor conduction time calculated with F wave latency were both nearly twice normal at the upper and lower extremities, indicating that the conduction velocity of peripheral and central nerves was remarkably delayed.

Moreover, pathology findings from peripheral sural nerve biopsy revealed drop-out of large myelinated fibres, thinning of myelin ovoid structures and red metachromatic deposits (which appeared brown in the toluidine blue stained samples) in non-fixed frozen sections, a specific finding of MLD (figure 1B). The same deposits appeared green under polarised light. Electron microscopy showed electron-dense deposits to be Schwann cells with a heringbone pattern (figure 1C), a disease-specific finding of MLD. In the fresh frozen muscle sections from the left biceps muscle, there were no abnormal increased mitochondria or ragged-red fibres.

ARSA activity in peripheral white blood cells (WBC) was significantly decreased at 10.0 (normal 98.3 ± 22.2) nmol/mg protein/h, while the following were all normal: α -galactosidase, β -galactosidase, α -glucosidase, β -glucosidase, β -hexosaminidase, β -hexosaminidase A, α -mannosidase, β -mannosidase, α -fucosidase and β -glucuronidase. Direct sequencing of the ARSA gene in genomic DNA from the peripheral WBC revealed c.203T>C (L68P) in exon 1⁵ and c.1226C>T (T409I) in exon 8⁶, so we

Figure 1 Specific MRI and pathological findings in metachromatic leukodystrophy. (A) Fluid attenuated inversion recovery (FLAIR), T2W, DW and ADC-map images of MRI showed symmetrical volume loss and diffuse demyelination in white matter. FLAIR and T2WI high signal images showing lesions in bilateral deep white matter around ventricles suggested demyelination change spreading from periventricular to subcortical white matter as suggested by the high signal on ADC-map images. (B) Brown coloured metachromatic depositions were detected in the toluidine blue stained non-fixed cryosection of a sural nerve biopsy. These metachromatic depositions are a specific finding of MLD and were much easier to see as green spots under polarised light. The bar represents 50 μ m. (C) Under the electron microscope, disease-specific herringbone patterned electron-dense deposits were observed in the cytoplasm of Schwann cells. The bar represents 10 μ m.

Table 2 Nerve conduction study

	CMAP (mV)	DL (ms)	MCV (m/s)	F latency (ms)	SNAP (mV)	SCV (m/s)
Median nerve						
Wrist	6.26	5.84				
Elbow	5.42	15.74	20.2	NE	NE	NE
Ulnar nerve						
Wrist	3.44	5.54				
Elbow (distal)	1.17	13.14	17.8			
Elbow (proximal)	2.99	16.00	38.5	63.8	NE	NE
Tibial nerve						
Ankle				55.6		
Popliteal	NE	NE	NE		—	—
Peroneal nerve						
Ankle	1.54	12.40				
Fibula head	10.0	22.70	23.3			
Popliteal	880.0	32.20	6.3	59.4		
Sural nerve	—	—	—	—	NE	NE

This study showed about that motor conduction velocity was about half that of normal, with almost normal CMAP voltage on the median, ulnar and peroneal nerves. F wave latency on the ulnar, tibial and peroneal nerves was nearly twice that of normal. SNAP was undetectable on the ulnar, tibial and sural nerves. CMAP, compound muscle action potential; DL, distal latency; MCV, motor nerve conduction velocity; NE, not evoked; SCV, sensory nerve conduction velocity; SNAP, sensory nerve action potential.

considered our patient had compound heterozygous mutations causing MLD.

The authors diagnosed MLD with autoimmune Hashimoto thyroiditis. We assumed that the patient's psychotic disorders were due to demyelination in deep white matter mainly caused by low ARSA activity and not to any other autoimmune encephalitis related to Hashimoto thyroiditis. Bone marrow transplantation is planned for this patient.

Differential diagnosis

- Mitochondrial disorders
- Hashimoto encephalopathy

- Chronic progressive multiple sclerosis
- Globoid cell leukodystrophy
- Adrenoleukodystrophy
- Schizophrenia.

Treatment

The patient is being considered for treatment with allogeneic haematopoietic stem cell transplantation.

Outcome and follow-up

The patient's mental deterioration progressed slowly over 6 months.

DISCUSSION

Adult MLD is rare compared with the more usual infantile and juvenile forms. Such patients are often treated for mental disorders such as schizophrenia before neurological symptoms become apparent. Baumann *et al* reported that there were two clinical forms of adult-onset MLD, the motor type and the psycho-cognitive type.⁷ The psycho-cognitive type often starts with behavioural abnormalities with mood changes and unusual social reactions, followed by progressive mental deterioration. Most such patients show no neurological symptoms for many years, and are only diagnosed when neurological signs appear or MRI is carried out. MRI in MLD shows diffuse bilateral and often symmetrical demyelination, initially limited to the periventricular areas. A recent report has shown that construction of ADC-map images might detect deposits of metachromatic substance in the intercellular space as restricted diffusions⁸ although it is possible those are T2 shine-through effect which presenting extracellular oedema with cell necrosis following demyelination and glial damages. Clinical diagnosis of this rare disease is sometimes difficult if the patient has complications causing encephalopathy or encephalitis. In the differential diagnosis of the present case, the authors considered chronic progressive multiple sclerosis (CP-MS), mitochondrial disorders and autoimmune Hashimoto encephalopathy because (1) there were significant psycho-cognitive symptoms, (2) CSF protein level was elevated, (3) EEG showed diffuse θ -activity and (4) serum antithyroid antibodies were positive. The CSF study showed a low IgG index and no MBP or oligoclonal IgG bands, indicating that multiple sclerosis was unlikely. Muscle biopsy showed no increased ragged-red fibres, excluding mitochondrial disorders. Assay for anti-NAE antibodies,³ which were all negative, was also helpful when considering the differential diagnosis. However, Hashimoto encephalopathy cannot be ruled out by lack of anti-NAE antibodies, even though a high prevalence and high specificity of anti-NAE antibodies in patients with Hashimoto encephalopathy was previously reported.³ These antibodies were detected in 68–44% of patients with Hashimoto encephalopathy,^{3–9} while MRI findings in patients with Hashimoto encephalopathy were sometimes normal or showed quite mild changes.¹⁰ Moreover, some reports described deep white matter involvement in various areas of the cerebral cortex, especially the temporal lobes, in patients with Hashimoto encephalopathy.⁴ However, these MRI findings are milder than those in patients with MLD.

Finally, the diagnosis in this patient was MLD coexisting with euthyroid Hashimoto thyroiditis.

Learning points

- MRI should be performed in patients with unexplained psychovegetative abnormalities and mental deterioration.
- The diagnosis of metachromatic leukodystrophy can be confirmed by genetic testing of disease-causing arylsulfatase A mutations.
- Hashimoto encephalopathy should be considered in patients with unexplained neuropsychiatric symptoms; anti-NAE antibodies as a specific diagnostic marker for Hashimoto encephalopathy can be helpful.

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