Adult-onset metachromatic leukodystrophy with compound heterozygous ARSA gene mutation presented with mania and cognitive decline

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Abstract

Adult-onset metachromatic leukodystrophy is often a diagnostic challenge to many clinicians. It may be presented with psychiatry symptom before other evidences of leukodystrophy are uncovered. We report a 53-year-old patient who presented with 7-year history of manic-like presentation in addition to progressive neurocognitive deterioration. Diagnosis was made eventually with neuroimaging. Mutational analysis showed compound heterozygous of ARSA gene. This case demonstrated the challenge in diagnosing this condition due to its complex neuropsychiatric presentation.

INTRODUCTION

Metachromatic leukodystrophy (MLD) is a type of inherited lysosomal storage disease. There are four types of MLD with varying onset age and courses (infantile, early juvenile, late juvenile and adult). Compared to young patients, patients with adult-onset MLD (A-MLD) experience chronic and insidious progression of the disease. MLD is an autosomal recessive disorder caused by homozygous ARSA gene mutation. It is a rare lysosomal storage disease caused by arylsulphatase A (ARSA) enzyme activity defect. The defect leads to loss of ability to degrade the galactosyl-3-sulfate ceramides. Neuropsychiatric symptoms are often the initial presentation and thus may lead to delay in diagnosis of the condition. A-MLD commonly has an insidious onset after 16 years old but rarely after 50’s. Cognitive impairment, emotional instability and bipolar disorder have been reported as the initial presentation, thus misdiagnosis is relative common. We presented a 53-year-old Malaysian-Chinese female with A-MLD whose initial presentation was manic-like symptom and rapid progressing dementia.

CASE REPORT

Mrs A was a 53 years old Chinese married woman with no past psychiatric history. She was an adopted child and no information of her biological parents was available. She managed a family owned Chinese restaurant and her role was the executive manager for the restaurant while her husband was the chef. She was diagnosed and treated for dyslipidaemia in the last two years and had past surgical history of uterine fibroid. Mrs A presented with manic-like symptoms at the age of 46 years. She had unrestrained spending spree on purchasing raw food material for the restaurant and began to borrow money from illegal loan creditors without her family’s knowledge. She then began to make mistakes in money transactions and the restaurant accounts. According to her family members, she was also easily emotional and had very labile affect. Mrs A had second-person auditory hallucination and delusion of infidelity that her husband had extra-marital affairs. There was also progressive language impairment. She initially did not have problem with naming, but the language deteriorated from hesitancy speech, word-finding difficulty, later incomprehensible sound and eventually mutes. There was also progressive short-term memory impairment. She had unsteady gait at the early course of her illness, as she needed support to keep the balance.

Mrs A had consultation with various hospitals
over the past several years but no definitive diagnosis was made. When Mrs AA was first seen in the neuropsychiatric clinic in Hospital Kuala Lumpur at age 53, she was cooperative and forthcoming. There was no focal neurological deficit but her gait was unsteady with small steps. There was no apraxia and frontal lobe sign was absent. Mental state examination at the time revealed Mrs A had significantly reduced verbal output. Her speech was minimal and mostly single word reply. Her mood was euthymic with labile affect. She did not exhibit overt psychosis during the interview. She had severe cognitive impairment in all domains (attention, visuospatial, memory, executive function and language). Her total score was 43/100 on the Neuropsychiatry Unit Cognitive Assessment Tool (NuCOG), which indicate very severe global cognitive impairment.

Routine laboratory investigations were unremarkable. Brain MRI revealed bilateral, symmetrical, confluent areas of increased T2 signal in the periventricular and deep white matter, with relative sparing of subcortical U fibres (Figure 1).

Further investigations were performed to look into the possibility of CADASIL and lysosomal storage disorders. NOTCH3 gene mutation was not detected. Plasma very-long-chain-fatty acid was not elevated. Blood lactate was 2.27mmol/L (normal range 0.50-2.20). Serum B12 and folate and urine organic acid test were unremarkable. Aryl-sulphatase (ASA) enzyme activity in leukocytes was low (44% from normal mean) with a level of 54nmol/hour/mg protein (reference range was 58.0-204.0nmol/hour/mg protein). B-galactosidase enzyme activity was within normal range. Skin biopsy for this lady was not performed. ARSA gene mutation analysis showed compound heterozygous mutation at c.1055A>G p.(Asn352Ser) in Exon 6 and c.1297C>G p.(Leu433Val) in Exon 8. Based on the ClinVar’s report from the National Centre for Biotechnology Information, United States National Library of Medicine, clinical significance of c.1055A>G p.(Asn352Ser) is pathogenic for in MLD.\(^7\) Mutation p.(Leu433Val) has not been reported in Human Gene Mutation Database (HGMD), however further bioinformatics analysis by Mutation Taster has predicted this mutation as pathogenic.

Based on findings from clinical, neuroimaging and laboratory investigations, diagnosis of A-MLD was made. Genetic counselling was given to her family members. Her children were not keen to pursue further genetic test. During the subsequent follow-up, Mrs A neuropsychiatric condition continued to deteriorate. Her gait gradually became worse and she was wheelchair bound by the time she was 54 years old. By then she was not able to take care of her own hygiene and required full nursing care.

![Figure 1. Axial (a) and coronal (b) T2-weighted MRI images show bilateral, symmetrical, confluent periventricular and deep white matter change with relative sparing of the subcortical U fibers (arrow).](image-url)
DISCUSSION

MLD is an autosomal recessive disorder caused by homozygous ARSA gene mutation. Homozygous ARSA gene mutation is generally associated with younger age of onset such as infantile and juvenile type of the disease. Compound heterozygous gene mutation is more common in later age of onset such as late juvenile and adult forms like in this case.\textsuperscript{3,5,9} A-MLD with heterozygous mutation of ARSA gene has been described in Germany, Belgium and Japan\textsuperscript{10-12} but this is the first case reported in Malaysia.

Mrs A’s initial presentations were manic-like behavioural and personality change in addition to progressive neurocognitive deterioration. Manic-like symptoms such as disinhibition and persistent euphoric mood have been described rarely\textsuperscript{5} and such presentation could easily be mistaken as primary bipolar mood disorder. Mrs A’s mood symptoms were labile affect and unrestrained spending spree. Despite the presence of mood symptoms, the presentation did not fulfil a diagnosis of manic episode. Psychotic symptom and personality change have also been reported commonly present in A-MLD and these may even be the initial clinical pictures.\textsuperscript{1,6,13} Detail history taking, neurological examination, and neuroimaging study are essential to lead to differential diagnosis of A-MLD.

In conclusion, A-MLD should be considered in the differential diagnosis of a person presented with young onset dementia with neuropsychiatric manifestations.

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