Research Paper
Article de recherche

Adult metachromatic leukodystrophy: disorganized schizophrenia–like symptoms and postpartum depression in 2 sisters

Hojka Gregoric Kumperscak, MD; Eduard Paschke, PhD; Peter Gradisnik, MD; Jernej Vidmar, BSc; Stanislava Umek Bradac, MD

Gregoric Kumperscak, Gradisnik, Vidmar, Umek Bradac — Department of Paediatrics, Maribor Teaching Hospital, Maribor, Slovenia; Paschke — Department of Paediatrics, University of Graz, Graz, Austria.

We describe the cases of 2 sisters with adult metachromatic leukodystrophy (MLD). Whereas one sister presented with disorganized schizophrenia–like symptoms as the initial manifestation of MLD, the other remained symptom free except for a 4-week period of postpartum depression. In both patients, there was some residual activity of leukocyte arylsulfatase A (1.7% and 5.5% of normal), and a marked increase in urinary sulfatides was present, as measured by tandem mass spectrometry. An arylsulfatase A pseudodeficiency was therefore excluded. The most common mutations of the adult phenotype, Ile-179-Ser and Pro-426-Leu, were not found. In the literature, only 1 case of adult MLD manifesting as disorganized schizophrenia–like symptoms has been described, whereas postpartum depression has been so far unknown as a presenting symptom of MLD.

Nous décrivons le cas de deux sœurs atteintes de leucodystrophie métachromatique (LDM) de l'adulte. Une sœur présentait des symptômes désorganisés semblables à ceux de la schizophrénie comme manifestation initiale de la LDM, l'autre ne présentait aucun symptôme, sauf une période de dépression postpartum de quatre semaines. Chez les deux patientes, on a constaté une activité résiduelle de l'arylsulfatase leucocytaire A (1,7 % et 5,5 % de la normale) et une élévation marquée de la présence de sulfatides dans l'urine, mesurée par spectrométrie de masse en tandem. On a donc exclu une pseudodéficience en arylsulfatase A. On n'a pas constaté les mutations les plus courantes du phénotype adulte, Ile-179-Ser et Pro-426-Leu. Dans les documents, on décrit un seul cas de LDM de l'adulte qui se manifeste sous forme de symptômes désorganisés semblables à ceux de la schizophrénie, tandis que la dépression postpartum était jusqu'à maintenant inconnue comme symptôme de manifestation de LDM.

Introduction

Metachromatic leukodystrophy is one of the most serious genetic demyelination disorders.[1] It is an autosomal recessive lysosomal disease characterized by demyelination of the white matter in the central nervous system and the peripheral nerves. The relevant gene is located on chromosome 22q13. The disease is caused by a deficiency of the enzyme arylsulfatase A, which hydrolyzes various sulfatides, including the major sulfate-containing lipids of the nervous system. Sulfatide accumulation can be found in the brain and peripheral nerves and nonneural organs (kidney and gallbladder).[2] The incidence of MLD is estimated to be between 1 and 5 cases per 100 000 population.[3]

There are 3 types of MLD: late infantile, juvenile and adult. The late-infantile form, which has its onset at the age of 1–2 years, is characterized by gait and behavioural disturbances. The course of the disease is rapid and the outcome fatal. The juvenile form, which has its onset between the ages of 3 and 15 years, displays a less distinct phenotype, varying from peripheral nerve involvement in younger children to learning problems and behavioural difficulties in older children.[4] It has a more protracted course. The most common presenting symptoms of the adult form, which begin in the

Correspondence to: Dr. Hojka Gregoric Kumperscak, Department of Paediatrics, Maribor Teaching Hospital, Child and Adolescent Psychiatry Unit, Ljubljanska 5, SI-2000 Maribor, Slovenia; fax 00386 2 331 23 93; hojka.gregoric@guest.arnes.si

Medical subject headings: arylsulfatases; depression, postpartum; leukodystrophy, metachromatic; schizophrenia, disorganized.

J Psychiatry Neurosci 2005;30(1):33-6.

Submitted June 13, 2003; Revised Nov. 18, 2003; Accepted Dec. 2, 2003

© 2005 Canadian Medical Association

late teens, are mental deterioration and behavioural abnormalities. Adult MLD has a slowly progressive course. Compared with the late-infantile and juvenile forms, the adult variant of MLD appears to be quite rare. To date, about 50 cases of confirmed adult MLD have been described. The mean survival for adult MLD is at least 12 years, which is longer than the survival in late-infantile MLD (3–4 years) and juvenile MLD (7–9 years).[2]

The diagnosis of MLD is based on arylsulfatase A activity in leukocytes or fibroblasts and on sulfatide excretion in the urine. An additional complication in the diagnosis of MLD is caused by the condition of arylsulfatase pseudodeficiency, in which low arylsulfatase A activity, but normal levels of urinary sulfatides, are found. Pseudodeficiency can be confirmed by a DNA assay for a specific allele.[2] To date, at least 87 arylsulfatase A mutations that are pertinent to MLD have been identified.[1] Among them, 11 have been correlated with the juvenile and adult forms of the disorder.[5] Some studies suggest a correlation between a single gene mutation and the psychiatric phenotype.[1]

Although MLD has been regarded as incurable, there have been some good results with bone marrow transplantation[6] and restoration of arylsulfatase A activity in human fibroblasts via retroviral vector–mediated gene transfer, the latter being still in the research phase.[7]

Case report

An 18-year-old girl was admitted to the Child and Adolescent Psychiatry Unit in the Department of Paediatrics, Maribor Teaching Hospital, Maribor, Slovenia, for suspected disorganized (formerly called hebephrenic) schizophrenia. A year before that, at the age of 17, she had begun to laugh without reason, and her behaviour had become silly and disorganized. Her emotional responses were inappropriate. She started grimacing and became paramimic and parathymic. She withdrew socially and began to shut herself in her room. She had auditory hallucinations, consisting of a running commentary on her behaviour. At that time, there were no changes in her school performance, which was already consistently below average; however, her school performance deteriorated 3 months before admission to hospital, when she became unable to do any schoolwork. She also became disoriented as to her whereabouts and got lost several times.

There had been no aberrations in her developmental milestones. Until recently, she had not had any diseases or needed any medical attention.

Her family history was interesting. She had a 24-year-old brother with moderate mental retardation according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV).[8] He had delayed developmental milestones and difficulties with walking and speaking. She also had a 25-year-old sister who, 4 years before, had had an episode of postpartum depression (according to DSM-IV criteria) that started a few days after she had delivered a baby. She had depressed mood and no interest in her baby or in any other activities. She showed decreased motor activity, complained about loss of energy and diminished ability to think and concentrate, and she reported feelings of worthlessness and guilt about being ill and not being able to take care of her baby. She cried constantly, had no appetite and suffered from insomnia. She recovered in a month without any antidepressants. The sister's school performance had been below average throughout all 10 years of her education, and she had been unable to find a job either before or after the episode of postpartum depression. She attended night school to become a cook and had achieved average success at the time of writing. There was no history of psychiatric disturbance before or after the episode of postpartum depression. The patient's mother had 7 half-siblings. Two had died, probably of pneumonia, at the age of 6 months. The third sibling was mentally retarded and probably had poliomyelitis at the age of 2 years. Otherwise there was no family history of psychiatric disorders.

At admission, our patient was disoriented regarding time, place, and person or identity. Her thought process was disorganized, and her behaviour was disorganized and uninhibited. She was paramimic and parathymic with blunted affect. Her rapport with others was poor and her speech monotonous, and her understanding of questions was poor. She had a poor attention span and reported auditory hallucinations, consisting of a running commentary on her behaviour, which she found pleasant. She described the hallucinations as a single young male voice, which was talking to her using short sentences, mostly encouraging her to do everyday tasks and commenting on her behaviour. She revealed a lack of initiative, had poor contact with reality and had no insight into her illness. She was incontinent of urine and had dyspraxia. Psychologic tests (Rorschach projective test and Bender Visual–Motor Gestalt test) revealed psychotic disturbance. The results of routine laboratory tests, including thyroid-stimulating hormone, vitamin B_{12} and folic acid, were normal. The findings of syphilis and HIV-1 serology were negative, as was serology for *Borrelia burgdorferi*. Levels of proteins in the cerebrospinal fluid were elevated (0.77 g/L). Electroencephalography showed abnormal bilateral synchronous, mainly theta activity, which was most prominent temporally.

According to DSM-IV diagnostic criteria, the patient's disease presented like disorganized schizophrenia (disorganized thought process and behaviour, flattening of the affect, auditory hallucinations and social dysfunction). These symptoms persisted for about 9 months without any marked signs of cognitive impairment, apart from poor attention and slowing in thought process. Therefore, treatment with small doses of an atypical antipsychotic, risperidone (1 mL twice a day), was initiated.

After 1 week of treatment, the patient stopped reporting auditory hallucinations. Although her behaviour was still disorganized, she was more willing to cooperate during the required medical examinations. Neurologic examination revealed positive pyramidal signs in the upper extremities. Tendon-stretch reflexes in the lower extremities were absent distally. Computed tomography revealed signs of advanced cortical atrophy, as well as symmetrical ventricular enlargement and periventricular white-matter hypodensity. Magnetic resonance imaging of the brain showed diffuse signal

hyperintensity of the white matter, especially in the periventricular area, as well as in the corpus callosum, cerebral atrophic changes and symmetrical ventricular enlargement. Electromyography showed slowing of nerve conduction velocities (NCV) (NCV of the peroneal nerve was 23 m/s [reference range 44–57 m/s]) and marked prolongation of F-wave latency. Visual evoked potentials showed a normal retinogram, but cortical responses had prolonged latencies with a normal response distribution. Somatosensory and acoustic evoked potentials were within normal limits. Abdominal ultrasonography revealed polyposis of the gallbladder.

Four weeks later, the disorganized and psychotic clinical picture diminished and the patient's cognitive impairment became increasingly obvious. Apart from poor attention and slowing of the thought process, memory (recollection and recent past) was disturbed the most. Therefore, neuropsychologic tests (Wechsler Intelligence Scale, Wechsler Memory Scale, Trail-making Test, Stroop Test, Hooper Visual Organization Test, Rivermead Behavioural Memory Test and the Controlled Oral Word Association Test) were carried out. The patients' full-scale IQ fell to within the range of severe mental retardation (according to DSM-IV criteria). There was a minor difference between the patient's verbal and performance IQ, favouring the former. The impairments were severe over the whole range of mental functioning. Attention processes, perception, executive functions, communication and motor skills were impaired. The patient's processing speed was very slow. Memory for verbally presented information and visual memory were found to be severely impaired. She could not independently perform any simple or routine operations. Therefore, an acetylcholinesterase (AChE) inhibitor was added to the therapy (galantamine, 4 mg, twice a day for 1 month, then galantamine, 8 mg, twice a day).

Taking into account the diagnostic findings of neurologic examinations, neuropsychologic tests, urinary incontinence and imaging, it was clear that there was most probably an organic disorder underlying the disorganized schizophrenia–like symptoms, which also caused later symptoms of dementia. Therefore, further tests were performed, focusing especially on inherited metabolic disorders.

The results of urine screening tests and screening for very long chain fatty acids in the serum were normal, excluding adrenoleukodystrophy and several disorders of peroxisomal function. Arylsulfatase A activity in leukocytes was markedly reduced (0.05 nmol/min per milligram [reference range 1.1–8.7 nmol/min per milligram]). Measurement of urinary sulfatides by electrospray ionization–tandem mass spectrometry[9] showed a 10-fold elevation of 609 nmol/L (reference range 5–148 nmol/L), thus confirming the diagnosis of MLD.

In the patient's sister, who remained clinically asymptomatic apart from the single episode described earlier, biochemical tests also showed clear arylsulfatase A deficiency in leukocytes (0.16 nmol/min per milligram) and markedly elevated sulfatides in urine (436 nmol/L), thus proving the presence of MLD. In accordance with their obligate heterozygosity, intermediate arylsulfatase A activity was found in both of our patient's parents. Our patient's mentally retarded older brother had normal arylsulfatase A activity and normal values of sulfatides in the urine. A preliminary search for mutations excluded the presence of the most common alleles associated with adult MLD, Ile-179-Ser and Pro-426-Leu on exons 3 and 8, respectively. A detailed genotype analysis of the entire family is currently underway.

Discussion

The symptoms of adult MLD include dementia, psychosis, behavioural abnormalities, ataxia, polyneuropathy and epileptic seizures.[10] Other psychiatric disorders can present with the following MLD symptoms: personality changes, depressive disorders, alcohol addiction, and worsening of school and/or work performance.[3]

There is much disagreement in the literature regarding the incidence of psychosis in adult MLD. Hyde et al[11] suggested that, in 53% of patients with adult MLD, psychosis is present and is often the initial manifestation. However, in most of the patients in that study, only arylsulfatase A activity was determined, which is insufficient for a definitive diagnosis of MLD. Cengiz et al[12] reported the cases of 3 sisters with adult-type MLD, 2 of whom were initially diagnosed as having schizophrenia. Hageman et al[2] state that psychosis is a less common symptom than previously suggested. In their group of 13 patients with confirmed adult MLD (in a case series dating from the period 1972–1992), the most common symptoms were ataxia and behavioural abnormalities, with only 1 patient having psychosis. The findings were similar in the group of 24 patients with confirmed MLD described in the literature, among whom only 4 were psychotic.[2]

Disorganized schizophrenia–like symptoms were the initial manifestation of MLD in our patient, and they persisted without any marked signs of cognitive impairment for at least 9 months. Then she got lost several times, and her school performance deteriorated. It is open to discussion whether her school performance deteriorated because of the disorganized schizophrenia–like symptoms or whether this was the first symptom of dementia. The differential diagnosis of dementia became problematic when disorganized and psychotic symptoms diminished after treatment with antipsychotics. We wondered whether the disorganized schizophrenia–like symptoms just masked dementia? The first symptoms of disease were disorganized and silly behaviour, disorganized thought process, inappropriate affect, social withdrawal, incongruous grimacing, outbursts of laughter without any apparent reason, paramimia, parathymia, auditory hallucinations, poor contact with reality and no prominent signs of cognitive impairment. All these symptoms can also be found with dementia; however, they usually occur later, have a gradual onset and are rarely all present at the same time. At some point, as MLD progressed, disorganized schizophrenia–like symptoms most probably masked dementia, but dementia was not the initial manifestation of MLD in our patient. To our knowledge, there is only 1 report of disorganized schizophrenia–like symptoms as the first clinical manifestation of MLD.[3]

The patient's sister, in whom the diagnosis of MLD was confirmed biochemically, had had an episode of postpartum

depression 4 years before. The literature describes some cases of adult MLD manifesting as major depression, but to our knowledge none of postpartum depression.[13,14] Further diagnostics, namely, imaging and electrophysiologic and neurocognitive testing are being carried out in the sister.

Our preliminary DNA analysis excluded the 2 most common alleles found in patients with adult MLD, and further studies will reveal whether the existence of a novel mutation in this family can explain the rare psychiatric symptoms in the 2 sisters. Some studies in the literature already suggest a correlation between a single gene mutation and the psychiatric phenotype.[1]

At present, it is hard to find a specific behavioural phenotype in both sisters. In order to do so, a longer period of observation is needed.

Little is known about the symptomatic treatment of psychotic symptoms and dementia in MLD. Our patient responded well to treatment with small doses of an atypical antipsychotic, showing no side effects. More questionable is the treatment with AChE inhibitors, which is only indicated in Alzheimer's disease.

The most important question still to be answered is how to treat the patient's sister with clinically silent MLD. Because this clinical silence is time-limited, she could be a good candidate for bone-marrow transplantation.

This report underlines the importance of metabolic diseases as a cause of what appears to be psychosis or schizophrenia-like or other psychiatric syndromes with rapid intellectual deterioration to dementia.[15]

Acknowledgements: The authors thank Blanka Kores Plesnicar, PhD; Olga Krajnc, MD; Brigita Lobnik, MD; Ignac Schmidt; Zlatan Turcin, MD; and Associate Prof. Alojz Gregoric, PhD, for their guidance, support and editorial comments.

Competing interests: None declared.

References

1. Tylki-Szymanska A, Berger J, Loschl B, Lugovska A, Molzer B. Late juvenile metachromatic leukodystrophy in three patients with similar clinical course and identical mutation on one allele. *Clin Genet* 1996;50:287-92.

2. Hageman AT, Gabreels FJ, de Jong JG, Gabreels-Festen AA, van den Berg CJ, van Oost BA, et al. Clinical symptoms of adult metachromatic leukodystrophy and arylsulphatase pseudodeficiency. *Arch Neurol* 1995;52:408-13.

3. Rentrop M, Hakk K, Freisleder FJ, Kissling W, Kockott G. Kindstotung und hebephrenes Syndrom bei metachromatischer Leukodzstrophie. *Nervenarzt* 1999;70:276-80.

4. Kaye EM. Update on genetic disorders affecting white matter. *Pediatr Neurol* 2001;24:11-24.

5. Figura K, Gieselmann V, Jaeken J. Metachromatic leukodystrophy. In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. *The metabolic and molecular bases of inherited disease*. 8th ed. New York: McGraw-Hill; 2001. p. 3695-724.

6. Navarro C, Fernandez JM, Dominguez C, Fachal C, Alvarez M. Late juvenile metachromatic leukodystrophy treated with bone marrow transplantation: a 4-year follow-up study. *Neurology* 1996; 46:254-6.

7. Rommerskirch W, Fluharty AL, Peters C, von Figura K, Gieselmann VAD. Restoration of arylsulphatase A activity in human-metachromatic leukodystrophy fibroblasts via retroviral-vector-mediated gene transfer. *Biochem J* 1991;280:459-61.

8. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 4th ed. Washington: the Association; 1994.

9. Whitfield PD, Sharp PC, Johnson DW, Nelson P, Meikle PJ. Characterization of urinary sulphatides in metachromatic leukodystrophy using electrospray ionization-tandem mass spectrometry. *Mol Genet Metab* 2001;73:30-7.

10. Kolodny EH. Metachromatic leukodystrophy and multiple sulphatase deficiency: sulphatide lipidosis. In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. *The metabolic basis of inherited disease*. 6th ed. New York: McGraw-Hill; 1995. p. 2693-739.

11. Hyde TM, Ziegler JC, Weinberger DR. Psychiatric disturbances in metachromatic leukodystrophy. *Arch Neurol* 1992;49:401-6.

12. Cengiz N, Ozbenli T, Onar M, Yildiz L, Ertas B. Adult metachromatic leukodystrophy: three cases with normal nerve conduction velocities in a family. *Acta Neurol Scand* 2002;105:454-7.

13. Ricketts MH, Amsterdam JD, Park DS, Yang RS, Portez RD, Zhang X, et al. A novel arylsulphatase A protein variant and genotype in two patients with major depression. *J Affect Disord* 1996;40:137-47.

14. Vella G, Loriedo C, Raccah R, Baldassare P, Paolillo A. Successful paroxetine treatment of major depression in an adult form of metachromatic leukodystrophy with cognitive disturbance. *Can J Psych* 1998;43:748-9.

15. Seidl D, Goebel HH, Scholz W. Late-onset metachromatic leukodystrophy: diagnostic problems elucidated by case report. *J Neurol* 1981;226:119-24.