

Familial metachromatic leucodystrophy as the cause of psychotic manifestations in young adults

Mieczysław Wender¹, Danuta Pruchnik-Wolińska²,
Włodzimierz Paprzycki³, Barbara Czartoryska⁴

¹Division of Neuroimmunology of the Institute: Center of Experimental and Clinical Medicine,
Polish Academy of Sciences

²Chair of Neurology, K. Marcinkowski School of Medical Sciences, Poznań

³Institute of Radiology, K. Marcinkowski School of Medical Sciences, Poznań

⁴Department of Genetics, Institute of Psychiatry and Neurology, Warsaw

We present two cases of metachromatic leucodystrophy (MLD) in a brother and sister, in whom the first signs of the disease appeared at adult age and manifested themselves by symptoms of mania and progressing dementia not accompanied by focal neurological symptoms...

Key words: metachromatic leucodystrophy, dementia, mania

Genetically determined metabolic disorders of the nervous system are rarely a cause of psychic disturbances in adults. One of the diseases that may constitute a diagnostic problem on the borderline between psychiatry and neurology is the metachromatic leucodystrophy (MLD). This disease is caused by the lack or defective activity of lysosomal aryl-sulfatase A, which results in an undue accumulation (storage) of sulfatides (cerebroside sulfates) in the nervous system and visceral organs, with a consecutive demyelination of both the central and peripheral nerves. MLD is usually a heredofamilial, autosomal-recessive condition. So far, a number of arylsulfatase A gene mutations responsible for MLD have been identified. The disease occurs more frequently in children. However, the first clinical symptoms may manifest themselves even as late as the age of twenty or so (late-onset forms). During the first years of this condition, the disease may manifest itself almost exclusively by psychic disturbances, mainly by a progradient dementia. Only after a long-term latency, neurological deficits become visible. Hence, some cases of MLD may be erroneously diagnosed as an early type of Alzheimer's dementia or even as schizophrenia, the latter - mainly in patients experiencing hallucinations and delusions (2).

In a synthetic review of Hyde et al. (6) it has been reported that until 1992 a total number of 129 cases of MLD have been verified (both adolescent and adult forms) and about 50% of these patients manifested psychic symptoms. Because of the known scarcity of this disease in adults we believed it justified to present two cases of MLD that occurred in a brother and sister.

Case report

Case No 1. A woman aged 21. The first symptoms of the disease appeared at the age of 18, when the patient, at that time a student of the 3rd year of a college experienced difficulties in learning, especially in remembering the newly acquired knowledge. The case history did not reveal any previous serious diseases. The dementia continued to progress, so that at the time of admission to the department of neurology (Medical Academy Poznań) in the third year of the disease, her intellectual ability judged by the Wechsler test was evaluated as being on the II - 40 level (word scale - II -55, wordless scale - II-37). Further psychological examination revealed a decreased potential within almost all functions of recent memory, a diminished analytical reasoning and conceptual as well as comprehensive thinking, a substantial slowing of learning capability and a reduced visual-motor coordination. The remote memory was only slightly reduced. The auto- as well as allo-orientation remained unchanged. Neurological examination did not show any abnormalities. Clinical observation did not reveal any behavioral changes. The patient did not complain about hallucinations or delusions.

Paraclinical investigations

SE- MRI - tomography: in the axial and vertical cross sections of T2 and PD dependent images - massive, diffuse hyperintensive (hyperdense) changes were seen. In T1 dependent images - hypointensive (hypodensive) areas were detected, located predominantly in the periventricular cerebral white matter, encompassing the whole of the optical adiation. This picture corresponds with a demyelinating process in the course of MLD (fig. 1 and 2)

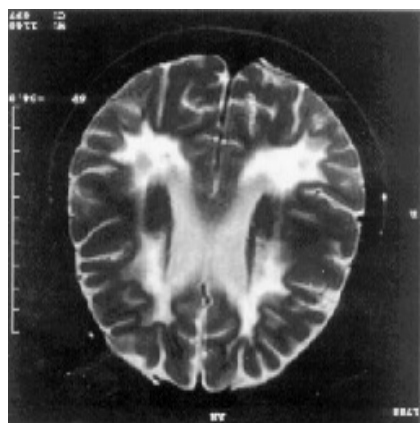


Fig. 1. Case No 1. A T2-dependent MRI-CT image of the axial brain section. Extensive demyelination areas in the form of irregular hyperdense foci around the cornua of the lateral brain ventricle.

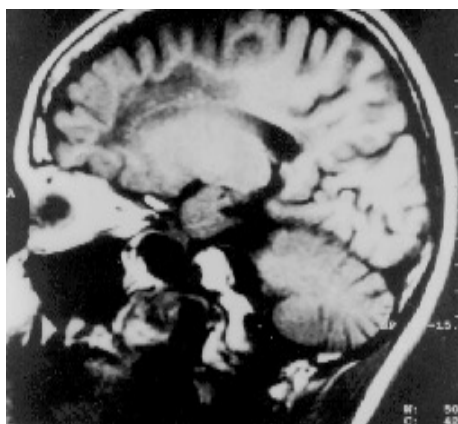


Fig. 2. Case No1. A T1 dependent MRI-CT image of the vertical cross-section. Around the cornua of lateral ventricles – irregular hypodensive areas corresponding with demyelination foci are seen.

Table 1

Lysosomal enzyme activities in blood leukocytes
 (Department of Genetics, Metabolic Laboratory, Institute of Psychiatry and Neurology, Warsaw)

Enzyme		Result nmol/mg prot/hr	Mean normal value ± SD
Arylsulphatase A (β ¹ AC)	Case 1	20.4	105 ± 30
	Case 2	16	
	Father	135.4	
	Mother	31.0	
Arylsulphatase A (β ² AC)	Case 1	25.5 nmol/mg prot/hr	262 ± 20
	Case 2	5.5 „ „	
	Father	23.4 „ „	
	Mother	10.0 „ „	
Beta galactosidase	Case 1	145.4	281 ± 40
	Case 2	11.4	
	Father	244.4	
	Mother	140.4	
Total beta glucosaminidase	Case 1	445.4	645 ± 35.9
	Father	200.4	
	Mother	566.4	
	Case 1	50.4%	
% of fermentable phase Arylsulphatase B	Case 1	39.4	19 ± 3.9
	Case 2	63.4	
	Father	61.4	
	Mother	64.4	
Alf mannosidase	Case 1	20.4	63 ± 5

The CT-image revealed an internal hydrocephalus within the lateral ventriculi as well as periventricular signs of atrophy, particularly around the frontal and occipital cornua of the ventricles.

EEG. The records taken at rest revealed considerable generalized distortions of the bioelectrical activity of the brain, along with numerous medium and high-voltage acute and theta waves of a frequency between 4 and 7/s.

The results of investigations of lysosomal enzyme activities of blood leukocytes are presented in Table 1.

On the basis of these results, we were able to definitively identify these conditions as a late form of MLD

Case No2. Male aged 36; brother of the patient denoted as case No 1. The anamnesis did not reveal any serious illness during childhood or adolescence. After completion of a workman school he worked as a house-painter. At the age of 21, while in military service, he manifested the first symptoms, which on retrospection may be estimated as a maniacal syndrome. Because of his behavioral disturbances, he was confined to

imprisonment for violation of military discipline. In the course of his further life his behavior grew worse; his aggressiveness and offensiveness increased. He kept destroying things in his surroundings, and developed losses of recent memory. At the age of 30 he was admitted to a district hospital for psychiatric observation. There, he was treated for affective psychosis in a maniacal phase and oligophrenia. Focal neurological symptoms were not found. The patient did not reveal any psychotic symptoms.

The state of the patient continued to deteriorate, so that a logical contact could no longer be achieved and a psychological examination was rendered impossible. The MRI-CT examination performed in the 15th year of the disease was not fully conclusive, because of the high-grade agitation of the patient. Nonetheless, in the T1-dependent image, an irregular hypodense zone was found within the periventricular white matter, which could account for demyelinating changes in this brain region. (Fig.3)

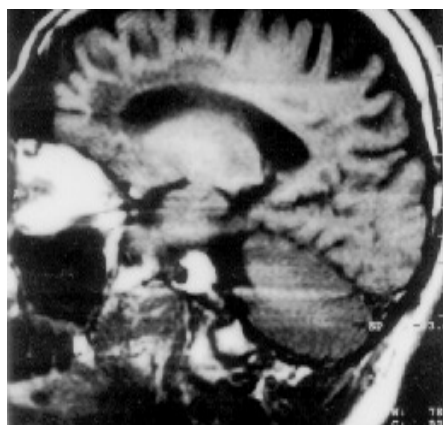


Fig. 3. Case No2. A T1-dependent MRI-CT image of the vertical cross-section of the brain. Around the frontal horn of the lateral ventricle, an irregular hypodense zone indicative of demyelination may be seen.

The significantly decreased activity of leukocyte lysosomal arylsulfatase A confirms the diagnosis of MLD.

Familial case history: Mother, 62 years old and father - 64, no kinship; healthy. Without any symptoms of abnormality in their neurological state. The activity of lysosomal enzymes at normal levels. Other members of the family did not or do not present any abnormalities in their health state (fig.4)

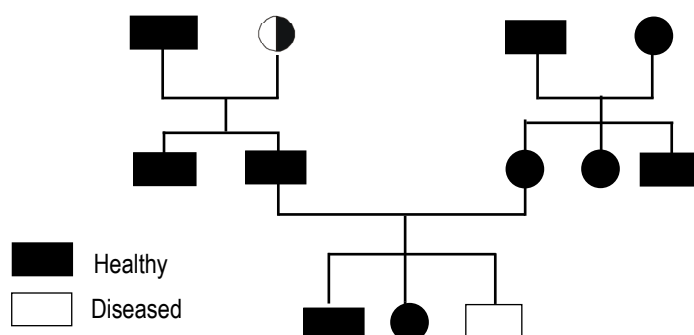


Fig.4. Genetic tree of the family. In the lower part of the tree – the above described patients; in the upper part – the assumed genetic pattern of their grandparents

Discussion

The herewith presented cases of late-onset familial MLD constitute a distinct example of diagnostic difficulties, which may be encountered in this disease. These problems may exist till the time when the psychic disturbances, in particular the symptoms of dementia, become accompanied by distinct focal, neurological signs. Demyelination in the central nervous system is the leading pathological process in MLD, which is responsible for the interruption of cortico-cortical and cortico-subcortical junctions, mainly in the frontal lobe (4).

The preponderance of psychotic symptoms over neurological deficits is not exceptional in the late-onset forms of MLD. Similar cases have already been described (3,4,5,6,7,8,9). In spite of the rare occurrence of the late form of MLD, it has to be taken into consideration in the differential diagnosis of dementia or in other unresolved psychotic disturbances in young adults. The importance of this aspect ensues clearly from the study of Alvarez-Leal et al. (1), who found a decreased activity of arylsulfatase A activity in 6 (23%) out of 23 cases suspected of schizophrenia. Thus, we can infer that storage of sulfatides in the CNS may be connected with the occurrence of psychic disturbances in this disease. The fact that these patients were unresponsive to the routine treatment with neuroleptic drugs has to be pointed out.

The modern techniques of neuroimaging (MRI-CT) as well as the easiness with which lysosomal enzyme activities can be measured make an *in vivo* diagnosis of MLD not only possible but also easily available. The lack of a positive family history (hereditary trait) in these cases does not seem to be of decisive importance for diagnosing of this disease. This opinion could be confirmed in our study.

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Adress:

Neuroimmunological Unit
Medical Research Center
60-355 Poznań
Przybyszewskiego 49 Str.
Tel. 8691565