Case report

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MYELINOPATHIA CENTRALIS DIFFUSA
(VANISHING WHITE MATTER DISEASE)
IN A FOUR-YEAR-OLD BOY

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SUMMARY

A four-year-old boy presented with moderate ataxia triggered by a minor head trauma several weeks ago. Discrepantly severe signal changes of cerebral white matter with almost CSF-isointense signal on all pulse sequences were detected at cranial MRI. Localized proton MR spectroscopy of cerebral white matter demonstrated an even decrease of all metabolites. Glycine was found elevated in CSF. This pattern of clinical history, MR imaging and spectroscopy features and elevated glycine in CSF is characteristic for a novel entity amongst the leukoencephalopathies of childhood. It was originally termed “myelinopathy centralis diffusa” and renamed “vanishing white matter disease” later.

Key words: leukoencephalopathy, childhood ataxia, glycine, myelinopathy centralis diffusa, vanishing white matter.

INTRODUCTION

When Hanefeld and coworkers in 1993 described a leukoencephalopathy in three children with “unique features on MR imaging and MR spectroscopy” this was the first report of a disease now recognized as a novel entity amongst the disorders of cerebral white matter in childhood [5]. After normal early development, affected children show a chronic-progressive motor deterioration with spasticity and ataxia and additional worsening following minor head trauma or febrile infection. Later the term “Myelinopathy Centralis Diffusa (MCD)” was proposed by Hanefeld [3], whereas van der Knaap et al. named it “Leukoencephalopathy with Vanishing White Matter” (VWM) [10]. Neuropathological characteristics have been identified [2]. The gene has been mapped to chromosome 3q27 [6], and mutations in the translation initiation factor eIF2B have been shown to be the cause of this condition [7].

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Case Report

History

A four-year-old boy presented with ataxia of acute onset eight weeks ago in the neurological outpatients clinic. The symptoms were preceded by a minor head trauma, the boy had stumbled over a carpet and had initially limped. He had been treated by an orthopedist as a traumatic origin was suspected. A fracture was excluded by x-ray of the right ankle. The joint was fixed by a bandage and the pain-symptoms improved. Recently, the patient’s parents had noted an intention tremor only of the right hand.

No previous serious diseases were reported. Pregnancy and childbirth were uneventful. He was the first born of a 36-year old mother, who had two previous miscarriages. Pregnancy and birth were uneventful. The patient had a history of mildly delayed motor development and therefore received ergotherapy. The boy sat without support at eight months and walked at 15 months of age. He had received speech therapy because of speech impediment. Despite his developmental delay he attended a normal kindergarten without any problems. The family has no history of neurological diseases nor previously unexplained causes of death.
Clinical Examination

The patient was free of pain upon examination. He showed a right sided ataxia with an overextension of the right knee as well as a staggering gait. The boy felt insecure when walking alone and therefore sought support. Moreover, his hand-coordination and fine motor coordination skills were slightly impaired. No signs of cranial nerve damage, no loss of sensation, no paralysis, no dysdiadochokineses were present, the muscular reflexes were normal, the Babinski sign was negative. The internal status was normal. He was understanding well, whereas his expressive speech was impaired.

Diagnostic Studies

Routine blood tests with assessment of glucose, calcium, phosphate, liver function, renal function, lipids, and uric acid as well as serum levels of lactate, pyruvate, carnitine, and ammonia were normal. Assessment of amino acids, organic acids, oligosaccharides and mucopolysaccharides in urine showed no abnormalities. No evidence for an infectious disease was found. Investigation of CSF revealed increased glycine (14.2 µmol/l [normal: 4.4-7.1 µmol/l]), but otherwise normal results. A chromosomal analysis, an EEG, an ECG, and an ophthalmological examination were all normal. Nerve conduction velocities and somatosensory evoked responses were normal.

The ergotherapeutical and physiotherapeutical status were consistent with ataxia with reductions in the vestibular system and in the boy’s coordination, with increased muscle tension. Ergotherapists found his manual skills and speech ability to be drastically reduced.

MR-Studies: The cranial MRI was diagnostic. There were typical alterations in the supratentorial white matter, which included a central and peripheral decrease of signal intensity in the T1-weighted and FLAIR images, and a CSF-isointense increase of signal intensity in the T2-weighted images. Normal myelination was found only in the capsula interna on the left and right hemispheric sides in the T1-weighted images. Additionally, the corpus callosum was decreased in volume due to secondary degeneration. The cerebellum was normally myelinated with some vermian atrophy. A further diagnostic
feature was the striking increase in signal intensity of the central tegmental tracts on the T2-weighted images (figure 1).

**MR-spectroscopy:** Fully relaxed short-echo time proton MR spectra (TR/TE = 6000/20 ms, 64 accumulations) were acquired with use of single-voxel stimulated echo acquisition mode (STEAM) localization frequency and the standard imaging headcoil at 2.0 T (Siemens Magnetom Vision, Erlangen, Germany) [4]. Spectral evaluation and quantification of absolute metabolite concentrations were accomplished as described [8]. Previous studies of regional age dependencies of cerebral metabolites provided age-matched controls [8].

A spectrum of parieto-occipital white matter showed almost normal proportions of all major metabolites, but an even decrease of their concentrations, as evident from comparison to a normal control spectrum (not shown). Quantitative analysis of absolute metabolite concentrations revealed a reduction of N-acetylaspartate to 4.6mM (6.9±0.6), creatine to 3.9mM (4.9±0.4), choline to 1.0mM (1.6±0.3) and myo-inositol to 2.8mM (3.7±0.6), (normal values given as mean ± SD) (figure 2).

**DISCUSSION**

A four-year-old boy presented with mild delay in motor and speech development and moderate ataxia triggered by a minimal head trauma. Cranial MRI demonstrated a discrepancy between severe leukoencephalopathy with extensive, homogenous and symmetric changes of cerebral white matter, which showed nearly CSF-isointense signal on all pulse sequences. Localized proton MR spectroscopy revealed an even decrease of all metabolites. Glycine was found elevated in CSF. All known disorders of lysosomal, peroxisomal, and mitochondrial as well as amino acid and organic acid metabolism were ruled out by extensive laboratory investigations. No evidence for an infectious disease was found. Neurophysiological studies documented normal function of peripheral nerves.

This pattern of clinical history, MR imaging and spectroscopy features and elevated glycine in CSF is characteristic for a novel entity termed “vanishing white matter disease” or, in the original report, “myelinopathia centralis diffusa”. Our patient has been diagnosed in an early stage of the disease. With ongoing course the leukoencephalopathy leads to an increasingly severe MRI signal change of white matter, which finally is indistinguishable from CSF in all pulse sequences. This is paralleled by a gradual loss of all metabolites in proton MR spectroscopy of cerebral white matter. After longstanding disease white matter spectra only show small signals from glucose and lactate, a pattern matching CSF [1, 10]. In fact histopathologic investigations revealed cystic degeneration of subcortical white matter with loss of myelin and spongy alterations leading to a gradual replacement of myelin by CSF [10]. Apoptosis of mature oligodendrocytes has been observed in active demyelinating lesions and seems to be the critical event in this disorder [2]. Affection of siblings and offspring of consanguineous parents suggested an autosomal-recessive mode of inheritance [5, 10]. Its molecular genetics basis has been unravelled only recently [5].

Amongst the hitherto unclassified leukoencephalopathies of childhood, myelinopathia centralis diffusa, or vanishing white matter disease, presents an important, recently delineated entity with characteristic clinical and neuroradiological features.

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**REFERENCES**


