MRI and MRS of Genetic Brain Diseases

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Introduction

Genetic brain diseases consitute a group of many different disorders, most of which are rare. As a group, however, they are not rare. They may become manifest at all ages with a preference for childhood and old age. Our focus is on the genetic brain disorders manifesting in infancy, childhood and adolescence.

Genetic brain diseases can be divided into two major categories: those predominantly affecting white matter and those predominantly affecting gray matter. The contribution of MR techniques has proven to be more important for white matter disorders than for gray matter disorders. The contribution of MRI and MRS can be found in the field of diagnosis, definition of new disorders, monitoring of progression of the disease and monitoring of effects of treatment.

Diagnosis

Several years ago, we have developed a so-called pattern recognition program for white matter disorders, based on a systematic, detailed analysis of many separate white matter structures for signal abnormalities (1). This program has proven to enhance the diagnostic information provided by MRI greatly. Most white matter disorders have a characteristic pattern of abnormalities, similar among patients with the same disorder or type of disorders, dissimilar from other disorders (2). The most important items in the pattern recognition process appear to be global distribution of abnormalities, lesions being confluent or isolated/multifocal, and presence or absence of additional gray matter lesions. The diagnostic contribution of MRI also depends on the stage of disease and is lower in beginning and end-stage disease.

If a gray matter disease is characterized by cerebral and/or cerebellar atrophy only, the diagnostic specificity of MRI is low. As soon as there are signal abnormalities in basal ganglia, cerebellar nuclei or brain stem nuclei, the diagnostic information increases.

The contribution of MRS to the diagnosis of genetic brain disorders is limited. The diagnosis usually comes from the assessment of a broad range of metabolites in body fluids (so-called metabolic screening), but in some cases, MRS may give a rapid and unexpected clue for the diagnosis, as in a creatine synthesis defect (3,4) and a defect in the metabolism of polyols (5).

Definition of new disorders

The cause of many progressive brain disorders in infancy and childhood remains unknown despite extensive laboratory investigations. It has been estimated that presently at least 60% of the cases with a white matter disorder in infancy or childhood remain unclassified and this figure is probably even higher for gray matter disorders. The last few years, MRI and MRS oriented research of several centers has been focused on the unclassified genetic brain disorders of childhood and several "new" disorders have been defined.

"Vacuolating leukoencephalopathy with subcortical cysts" (VLE) is a disorder with an autosomal recessive mode of inheritance. MRI shows a diffuse involvement of the cerebral white matter with relative sparing of corpus callosum, internal capsule and brain stem, and with subcortical cysts, always in the anterior temporal area, often also in the frontoparietal area (6). Results of a genetic linkage study are underway.

"Cerebellar ataxia with central hypomyelination" (CACH) (7) or "vanishing white matter" (VWM) (8) is also a disorder with an autosomal recessive mode of inheritance. MRI shows diffuse involvement of the cerebral white matter, of which parts show signal characteristics of CSF. MRS of the white matter shows a CSF spectrum. At autopsy, a leukoencephalopathy with rarefaction and cystic degeneration is found. Genetic linkage analysis revealed a gene locus on chromosome 3q27 (9).

The clue for the existence of a creatine synthesis defect came entirely from MRS (3). Images in this autosomal recessive disorder reveal either no abnormalities or basal ganglia lesions. MRS reveals an almost total absence of creatine. The basic enzyme defect has been elucidated (4). Creatine monohydrate treatment leads to clinical improvement and appearance of a creatine peak in brain spectra.

The clue for a defect in the metabolism of polyols also came entirely from MRS (5). Images revealed a white matter disorder. MRS of the brain revealed large signals of unknown origin between 3.5 and 4.0 ppm, which could subsequently be identified as representing ribitol and arabitol. The basic enzyme defect has not yet been elucidated.

Monitoring

Monitoring of progression of disease by means of MRI and MRS may be important when making decisions in treatment and in the evaluation of results of treatment. One example is found in presymptomatic and early symptomatic X-linked adrenoleukodystrophy, in which it has to be decided whether and when bone marrow transplantation is performed (10). Another example is found in the creatine synthesis defect, in which creatine monohydrate supplementation is monitored by MRS of the brain (3,4).

References

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