Genetic Dysregulation and White Matter MR Phenotype

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The brain is an organ with a highly complex functional topography. Different areas have different functions and need different connections. They have specialized cellular composition and organisation. They use specific chemicals for communication. There are differences in metabolism and in energy demands between different areas. Chemical composition and antigenic make-up differ. There are, of course, many more differences.

Already at microscopic examination the differences are obvious for gray matter structures, such as the cerebral cortex and central nuclei, but there must be similar differences for the white matter in different areas. Similar cells in different areas are not necessarily identical. Cortical astrocytes are different from white matter astrocytes and most likely are astrocytes in different white matter areas not identical. Myelin in the deep cerebral white matter is not necessarily exactly the same as myelin in the U-fibers and myelin in the brain stem.

The complex topography of the brain is reflected in complex patterns of selective vulnerability of brain structures to various adverse influences. These patterns of selective vulnerability can be visualized by MRI and form the basis of the MRI interpretation process called MRI pattern recognition. It is striking that both acquired disorders and genetic defects are often associated with highly consistent patterns of MRI abnormalities or “MRI phenotypes”. The consistent differences concern both large and small structures and substructures. Apparently, specific structures and parts of structures have an individual vulnerability for specific dysregulations and defects.

“Patterns of selective vulnerability” or “MRI phenotypes” can be used in the diagnostic process to recognize different disorders. In the early nineties, we developed an MRI pattern recognition system for white matter disorders. Over the years, the system evolved and became more complete, including information on many details. At present, most MRI patterns related to the many known white matter disorders have been defined and the variability of these patterns has been studied.

In addition, novel disorders can be detected by their MRI phenotype. Despite the fact that there are many known etiologies for white matter disorders, both acquired and genetic, the cause remains unknown in substantial numbers of patients. We have applied MRI pattern recognition to large groups of patients with a leukoencephalopathy of unknown origin and have defined multiple novel MRI phenotypes, including

- megalencephalic leukoencephalopathy with subcortical cysts (MLC)
- vanishing white matter disease (VWM), also called childhood ataxia with central hypomyelination (CACH)
- hypomyelination with atrophy of the basal ganglia and cerebellum (HABC)
- leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL)
- congenital cytomegalovirus (CMV) infection

We have used the MRI phenotypes to select patients and families eligible for genetic linkage studies and have found the genes for MLC, VWM and LBSL. The MRI phenotypes associated with these genetic defects have proven to be so consistent and homogeneous that these diseases can be recognized solely by their MRI phenotype.

The basis of the selective vulnerability of individual structures and parts of structures for specific adverse influences is not understood. Insight into the mechanisms behind the MRI phenotypes would greatly enhance our understanding of the pathophysiology of diseases.

Similarities in MRI phenotypes may reflect similarities in basic defects or pathophysiological mechanisms. This is true for both genetic and acquired disorders. The similarities between MR phenotype of MLC and merosin-deficient congenital muscular dystrophy suggested a relationship between the MLC1 protein and the dystrophin-glycoprotein complex, which could be confirmed. The MRI phenotype of congenital CMV infection and defects in the gene *RNASET2* are indistinguishable, which points to sharing of pathophysiology. The same is true for congenital infections and Aicardi-Goutières syndrome.