# 18q- syndrome and white matter alterations.

O Gabrielli, G V Coppa, I Carloni and U Salvolini

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# LETTERS

## 18q− Syndrome and White Matter Alterations

Alterations of the cerebral white matter due to specific genes directly involved in the central nervous system myelination processes have been recently published (1, 2). In particular, in a recent issue of *AJNR*, Loevner et al (2) described alterations of the white matter in 10 of 16 patients with 18q− syndrome; they hypothesize that these alterations are secondary to the involvement of one of the myelin basic protein genes. As we have reported (3), we observed alterations of the white matter in about 50% of patients bearing different malformation syndromes (27 of 56 cases). None of them was affected by 18q− syndrome. For this reason, we considered the alterations of the white matter an aspecific and frequent finding.

Therefore, at the present time, it seems difficult to frame these alterations into a well-known genetic transmission even though we cannot exclude the possibility that the white matter alterations observed by Loevner et al are caused by the involvement of a myelin basic protein gene. As the authors also affirm, it would be imprudent to draw final conclusions; the described alterations were not present in the totality of the 18q− subjects, but in 10 of 16.

Only the longitudinal magnetic resonance (MR) examination (to verify the persistence or the appearance of the white matter alterations in those subjects who had negative findings at a first control study) and a careful genetic analysis will enforce the hypothesis of the involvement of the myelin basic protein gene as a direct cause of the white matter alterations in patients with 18q− syndrome.

Orazio Gabrielli
Giovanni V. Coppa
Ines Carloni
*Department of Pediatrics*

Ugo Salvolini
*Department of Neuroradiology*

*University of Anona (Italy)*

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*Reply*

We appreciate the interest of Dr Gabrielli et al in our report of white matter findings on MR images in patients with 18q− syndrome. We agree with their comments that alterations of white matter are a nonspecific finding. Abnormalities of myelin can be acquired or can be caused by a wide variety of metabolic and genetic defects, none of which are "specific" in the sense that the defects are widespread. Knowledge and understanding of these defects, however, is important for understanding disease pathophysiology. The clinical and pathologic abnormalities in 18q− syndrome, although quite variable, are clearly caused by deletion of a portion of chromosome 18. This implies that absence of specific genes on chromosome 18 is the cause of the mental and developmental delay, growth deficiency, craniofacial dysmorphism, and other abnormalities that define this syndrome. However, many of these clinical abnormalities are also found in other syndromes, so they too are nonspecific.

The fact that other malformation syndromes also cause white matter changes does not weaken this argument, since the white matter changes may be caused by entirely different molecular mechanisms. Our speculation that deletion of the myelin basic protein (MBP) gene might be involved in the pathophysiology of the white matter abnormalities in 18q− is an attempt to make the clinical features of this syndromes more understandable at the molecular level, although a more indirect mechanism might also be possible.

While Gabrielli et al make a valid argument that white matter changes may be a nonspecific finding in 18q− syndrome, because of the location of the MBP within the deletions that are present in patients with 18q− syndrome, we felt that it was appropriate to investigate whether the hemizygosity of myelin basic protein would result in hypomyelination in all patients affected with 18q− syndrome. We were specifically testing whether the hemizygosity of MBP was a primary cause for hypomyelination previously reported in a handful of patients with 18q− syndrome (1–4). As we and Gabrielli et al noted, this did not appear to be the case, since many but not all of our 16 patients studied showed abnormal white matter. Therefore, although the hemizygosity of the MBP may lead to a susceptibility to white matter changes, white matter changes are not a universal feature of 18q− syndrome. Furthermore, the white matter changes do not appear to be the primary cause of the mental and developmental delay observed in this particular group of patients.

Another reason for the MR evaluation of patients with 18q− syndrome was that the characterization of central nervous system abnormalities has lagged behind the delineation of the clinical features of this syndrome.

We agree that longitudinal MR examinations to verify the persistence and/or progression of white matter alterations in patients who demonstrate white matter disease, and to evaluate the development of white matter changes in subjects with negative findings on initial MR exam, are necessary to enforce the hypothesis of involvement of the MBP gene as a cause of the white matter alterations in 18q− syndrome. Clearly further research will be needed to test this hypothesis.

Laurie A. Loevner
*Department of Radiology*
*University of Pennsylvania Medical Center*
*Philadelphia*

Joan Overhauser
*Department of Biochemistry*
*Thomas Jefferson University*
*Philadelphia, Pa*

John Kamholz
*Department of Neurology and Molecular Medicine*
*Wayne State University School of Medicine*
*Detroit, Mich*

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*Comment*

MR findings in the central nervous system of patients with a deletion of the long arm of chromosome 18 (18q−) are diffuse bilateral symmetric T2 hyperintensity most prominent in the periventricular regions. The cerebellum, brain stem, and corpus callosum are spared. The basis for the white matter abnormalities is undetermined. Changes in white matter may be primary or secondary. Secondary alterations are due to abnormalities of cortical neurons with secondary axonal and myelin abnormalities. Primary myelin abnormalities may occur when myelin is not laid down in the normal fashion (myelin hypoplasia). When there are defects in the metabolic turnover of myelin, then dysmyelination (leukodystrophy) results. The classic examples of metachromatic leukodystrophy and Krabbe leukodystrophy are associated with a lysosomal enzyme defect which prevents appropriate catabolism of myelin components. Myelin may be destroyed after it is normally formed as occurs with classic demyelinating diseases such as multiple sclerosis.

The 18q− syndrome is associated with a spectrum of neurologic abnormalities including hypotonia, mental retardation, seizures, autism, behavioral problems, developmental delay, strabismus, and nystagmus. All of these findings cannot be explained by abnormalities of myelination. In the case reports on 18q− syndrome, the imaging findings do not suggest a progressive demyelinating disorder, and clinically there is not a progressive neurologic deterioration. Dysmyelinating conditions do show progressive neurologic deterioration and myelin breakdown, although the pace of the change may be different depending on the type of leukodystrophy. In 18q−, normal myelination has not been confirmed in infancy, therefore this syndrome is not that of a classical demyelinating condition, defined by the presence of normal myelination followed by demyelination. Imaging in 18q− shows that myelination is present in the brain stem, cerebellum, and corpus callosum, therefore this is not a primary generalized deficiency of myelin. If a major gene involved in the formation of myelin was deleted, one would expect that all of the myelin in the central nervous system would show an abnormality. Because MR shows changes in deep gray matter, abnormalities of cortical gray matter may also exist but be below the level of MR detection. Certainly the significant mental retardation in this syndrome would be consistent with a neuronal abnormality. Therefore, changes in white matter could be secondary to a decreased number of neurons (axons) with consequent hypomyelination.

Unfortunately, there is very little pathologic evidence to correlate with the interesting MR images. The report by Felding et al describes the pathologic findings in an abbreviated manner and suggests that the "cerebral white matter was reduced with delayed myelination, impaired migration and slight hydrocephalus." The authors did not describe evidence of myelin degeneration, and of course delayed myelination may be present with impaired neuronal migration. We are left in a quandary at this point in time because of lack of firm documentation correlating the MR findings with specific structural or biochemical evidence of a primary abnormality of myelin. Although an interesting hypothesis has been proposed suggesting that the MBP gene and its gene product may play a role in the pathogenesis of this syndrome, there is no firm evidence that 18q− is a dysmyelinating condition.

L. E. Becker
*Departments of Laboratory Medicine and Pathobiology and Pediatrics*
*University of Toronto (Ontario, Canada)*