OBSERVATION

Vitamin D–Dependent Rickets as a Possible Risk Factor for Multiple Sclerosis

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Background: Vitamin D–dependent rickets type I (VDDR I) (OMIM 264700) is a rare hereditary condition caused by a mutation in *CYP27B1*. Vitamin D is emerging as an important risk factor for susceptibility to multiple sclerosis (MS), but there have been no studies on the possible association between hereditary rickets and this disease.

Objective: To investigate the association between VDDR I and MS.

Design: Case studies.

Setting: Haukeland University Hospital, Bergen, Norway.

Patients: Three patients in 2 families with a co-occurrence of VDDR I and MS.

Results: All 3 patients had VDDR I verified by genetic testing and fulfilled the Poser criteria for MS. Two of the patients have undergone magnetic resonance imaging, which confirmed the diagnosis of long-lasting MS.

Conclusions: Vitamin D–dependent rickets type I is a very uncommon genetic subtype of rickets. We have identified 3 patients with this disease who later developed MS. We propose that VDDR I and possibly other hereditary rickets mutations that influence vitamin D metabolism could be risk factors for this disease.

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VITAMIN D–DEPENDENT RICKETS type I (VDDR I) (OMIM 264700) is a rare hereditary condition caused by a mutation in *CYP27B1* (OMIM 609506), located on chromosome 12q13.1-13.3. The active form of vitamin D, 1,25-dihydroxycholecalciferol, is produced by a 2-step hydroxylation: first at the 25 position in the liver by the mitochondrial cytochrome P450 27A1 isozyme and then at the 1α position in the kidney by the cytochrome P450 27B1 isozyme. The cytochrome P450 27B1 isozyme is the key enzyme in determining the rate of 1,25-dihydroxycholecalciferol production. The cause of multiple sclerosis (MS) is unknown, but environmental factors seem to act in concert with genetic susceptibility. Vitamin D is emerging as an important cofactor in the development of this disease.[1] Thus, it is possible that people with deficits in vitamin D metabolism have an increased susceptibility to MS. We describe 3 patients with VDDR I with mutations in the *CYP27B1* gene who later developed MS.

REPORT OF CASES

PATIENT 1

Patient 1 is a 57-year-old woman who presented with VDDR I in early childhood. Nine exons of the *CYP27B1* gene were analyzed and we found that the patient was homozygous for the c.1166 G>A (p.R389H) mutation in *CYP27B1*, a well-known rickets mutation. She experienced her first neurological symptoms in 1963 in the form of spastic paraparesis and visual field defects. She finally had relapsing-remitting MS diagnosed in 1974. She fulfilled the Poser MS criteria with more than 2 attacks and objective clinical evidence of 2 or more lesions.[2] Her cerebrospinal fluid was consistent with MS (increased IgG index and pleocytosis). Her illness has had a secondary progressive form since 1995. Magnetic resonance imaging findings from 2002 were consistent with long-lasting MS (**Figure 1**).

PATIENT 2

Patient 2 is a 54-year-old woman and the younger sister of patient 1. She also presented with VDDR I in childhood. Like her sister, patient 2 was homozygous for the c.1166 G>A (p.R389H) mutation in the *CYP27B1* gene. She experienced 1 episode of ataxia and tremor in 1967 and had optical neuritis diagnosed in 1976 and relapsing-remitting MS diagnosed in 1977. She fulfilled the Poser MS criteria with more than 2 attacks and objective clinical evidence of 2 or more lesions.[2] Her cerebrospinal fluid was consistent with MS

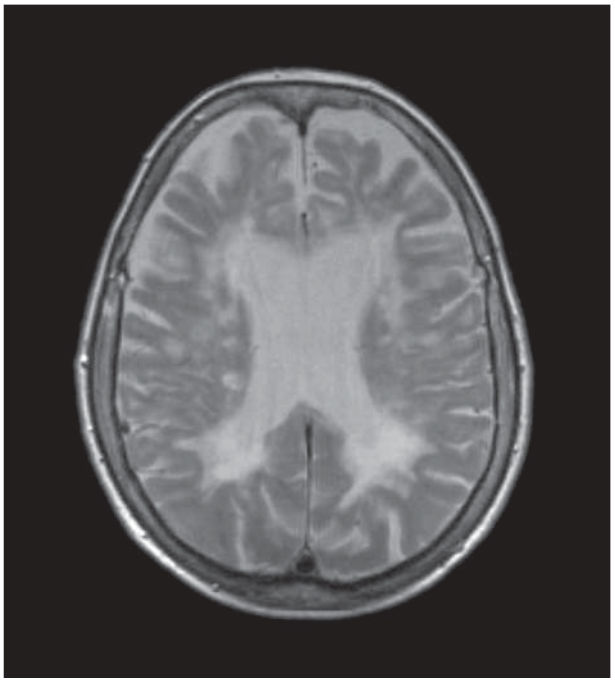

Figure 1. T2-weighted axial brain magnetic resonance image of patient 1 showing confluent and focal high-signal white matter lesions as well as central cortical atrophy consistent with long-lasting progressive multiple sclerosis.

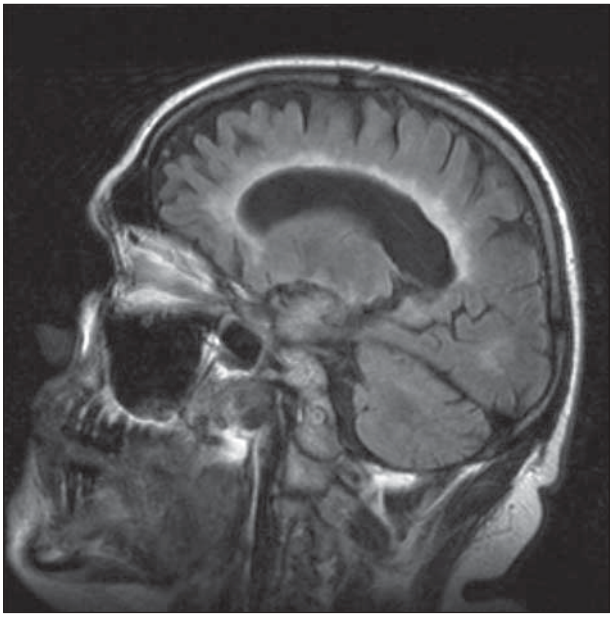

Figure 2. Sagittal fluid-attenuated inversion recovery brain magnetic resonance image showing high-signal lesions in an atrophic corpus callosum as well as generalized cortical atrophy consistent with advanced multiple sclerosis.

(increased IgG index, pleocytosis, and oligoclonal bands). Her disease has had a benign course and she has refused to undergo magnetic resonance imaging.

PATIENT 3

Patient 3 is a 54-year-old woman. She is the third of 6 children and presented with VDDR I in her childhood. She had 1 sister who also had VDDR I but who died from cancer. The coding regions of the *CYP27B1* gene were sequenced. The patient was compound heterozygous for the c.1166 G>A (p.R389H) and c.1320_1321ins CCCACCC mutations in *CYP27B1*. She temporarily experienced walking difficulties in 1982 during her first pregnancy. Her symptoms have progressed since 1984 and she has used a wheel chair since 1988. She also has visual problems and moderate paresis in both arms. Results from a clinical evaluation at our department in 2003, including cerebrospinal fluid examination, visual evoked potential response, and magnetic resonance imaging, confirmed relapsing-remitting MS with secondary progression (**Figure 2**).

COMMENT

We have observed 3 patients in 2 families with cooccurring VDDR I and MS. Multiple sclerosis has a prevalence of 1.5 per 1000 people in Norway.[3] The prevalence of VDDR I in Norway is unknown, but it is a very uncommon disease. We have identified 3 patients with VDDR I at Haukeland University Hospital, which serves 460 000 people. The patients were identified by searching in the electronic journals for individuals with VDDR I diagnosed during the last 10 years. Recently, promotor polymorphisms in *CYP27B1* have been shown to be associated with a number of autoimmune disorders, such as Addison disease, Hashimoto thyroiditis, and type 1 diabetes mellitus.[4] There have been no studies of the association between polymorphisms in *CYP27B1* and MS. Whole-genome linkage screens have not, however, confirmed an association between MS and the 12q13.1-13.3 region.[5]

Epidemiological studies have suggested a correlation between the prevalence of MS and vitamin D deficiency. High circulating levels of vitamin D are associated with a lower risk of MS and animal studies have shown that 1,25-dihydroxycholecalciferol has an immunosuppressive effect in experimental autoimmune encephalomyelitis.[1,6] The patients in our case series have been given cholecalciferol (vitamin D) supplements since childhood. Blood samples from 2 of the patients were available and they had normal and above normal levels of 1,25-dihydroxycholecalciferol. This could indicate early childhood or the intrauterine period as the main susceptibility period for low levels of vitamin D. However, we found no reports on the association between hereditary rickets and MS. Our findings of 3 patients with VDDR I and MS could indicate that VDDR I and possibly other hereditary forms of rickets are risk factors for this disease. Although the VDDR I mutation is rare in most parts of the world, it has been estimated to affect 1 of 2916 children born in the Saguenay-Lac-St-Jean region in Quebec, Canada.[7] Thus, this region could be of particular interest for studies on this possible association.

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Announcement

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