Vitamin D status and vitamin D receptor gene Fok1 and Taq1 polymorphisms in Portuguese patients with multiple sclerosis

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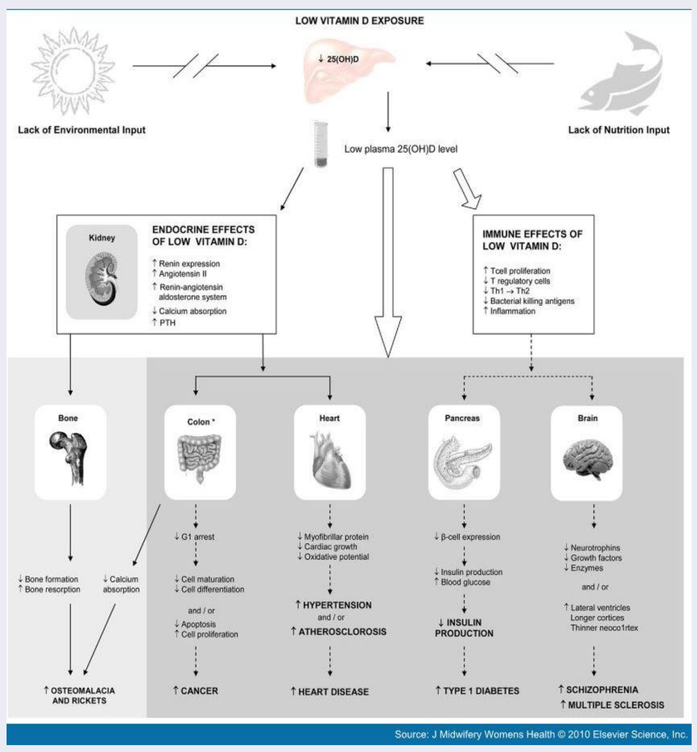
Background



Multiple Sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system. Its prevalence is dependent on geographical localization. Limited sunlight exposure, the principal source of Vitamin D synthesis, is considered an environmental risk factor, supporting the hypothesis that vitamin D plays a central role in the disease pathogenesis.

Although vitamin D is classically known as a central player in calcium and bone metabolism, recently important immune modulator effects have been reported (e.g. it inhibits the production of pro-inflammatory cytokines such as interferon gamma). Vitamin D acts via the vitamin D receptor (VDR), a nuclear receptor that is expressed in multiple immune cell types, including activated CD4+ and CD8+ T lymphocytes, APC, DC and B lymphocytes. Various single-nucleotide polymorphisms (SNP) in the VDR gene (Fok1, Apa1, Taq1 and Bsm1) have been described, and a functional impact of Fok1 polymorphism on the immune response has been demonstrated [1]. In the last years several studies have addressed the association of these VDR polymorphisms with MS, but with inconclusive results [2-5].

Aim: To investigate the association of Fok1 and Taq 1 with MS in a group of Portuguese patients and to study vitamin D status in the same group of patients.

Patients and Methods

A total of 426 MS patients, from the outpatient neurological clinic of Centro Hospitalar do Porto - Hospital de Santo António, and 261 ethnicity-matched controls were studied.

Clinical/demographic data	MS patients
Number of patients	426
Sex ratio (F/M)	275/151
Disease course (PP/SP/RR)	40/43/343
Mean disease duration, yr (range)	11.1 (1-47)
Mean age at onset, yr (range)	30.0 (6-60)
Median EDSS	3.1
Median MSSS	3.4

Genomic DNA was obtained from Proteinase-K treated peripheral blood leukocytes by using a Salting-Out procedure.

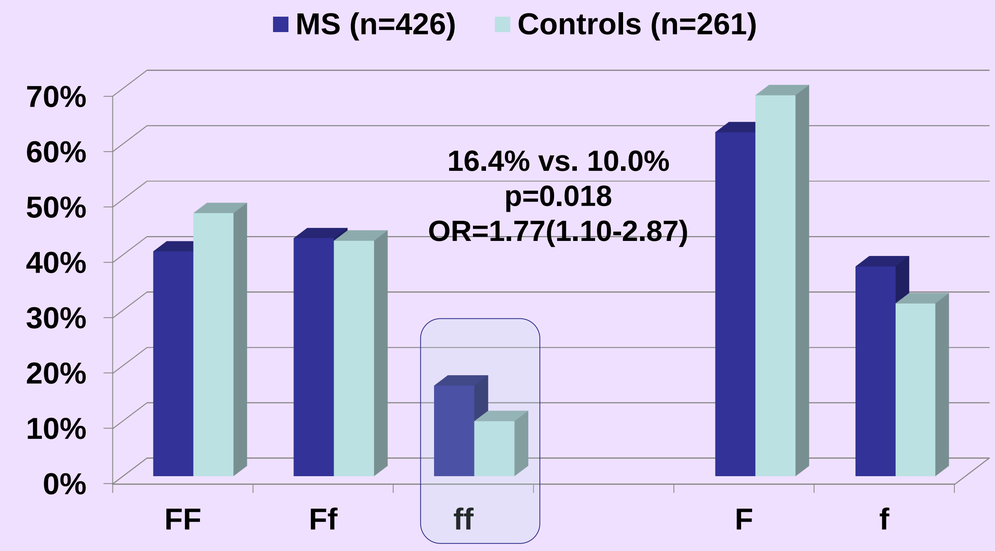
- Fok1 and Taq1 polymorphisms genotyping was performed using a PCR-based TaqMan Genotyping Assay.
- Serum 25(OH)D levels were available for only 154 MS patients (36.2%) and were determined using an electrochemiluminescence immunoassay. Serum 25(OH)D levels were classified as deficient when 25(OH)D<25nmol/L and insufficient when 25>25(OH)D <50 nmol/L.

Statistical Analysis

Differences in frequencies of Fok1 between MS patients and control subjects were evaluated using the Chi-Square and Fisher's exact test. Spearman correlation analysis was used to assess the relationship between vitamin D levels and disability (EDSS and MSSS). All analyses were done using PASW Statistics v18 software.

Results

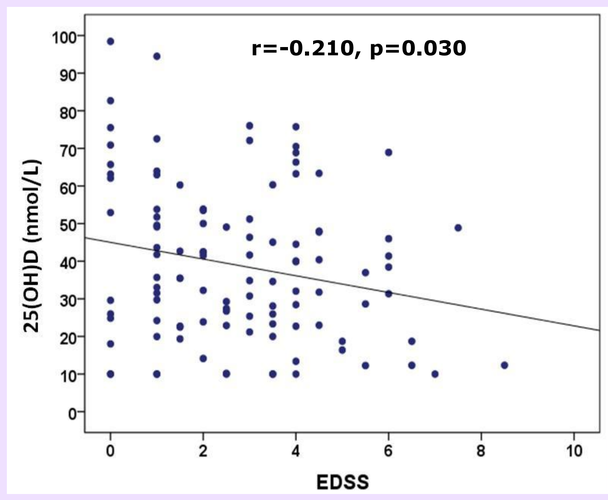
❖ The Fok1 ff genotype frequency was significantly higher in patient's group compared to controls.

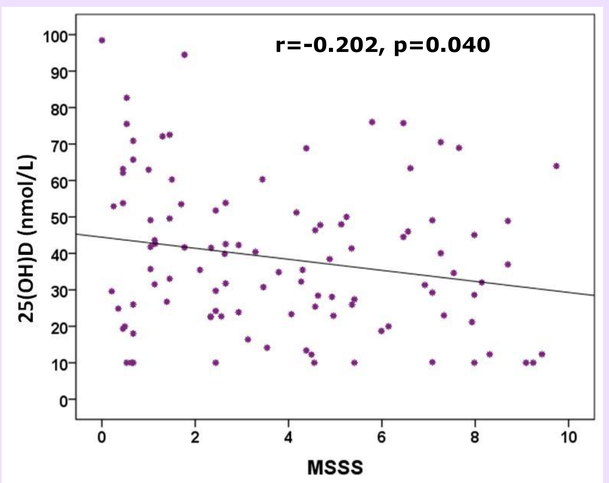


❖ No significant associations were found for the Taq1 polymorphism.

❖ Serum 25(OH)D levels revealed vitamin D deficiency or insufficiency in 66.9% of the patients.

❖ A negative correlation between vitamin D levels and disability was found.





Discussion

Contrary to previous studies from the UK, Australia and the Netherlands [2,5,6], our results document an association of the VDR gene polymorphism Fok1 with an increased risk of developing MS, in Portuguese patients. However, it should be kept in mind, that the functional impact of this VDR polymorphism is uncertain, and the reported association could well be the result of genetic linkage or other indirect effects. Assuming a role for VDR in MS susceptibility, geographical latitude could be a factor influencing the differences reported in the literature. Further studies, in different populations, are warranted. Future clinical and experimental studies on vitamin D and MS should take the Fok1 VDR polymorphism into account, to further clarify their role in MS susceptibility.

References

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