Fact sheet vitamin D / sun and Multiple Sclerosis

Background

The frequency of MS shows a clear north -south gradient. In addition, there are fewer incidences of MS in coastal regions compared to the inland. The number of cases in Asia and Africa are low compared to Western industrialized countries; that is by up to two orders of magnitude. It is evident from these observation that MS-frequency depends on latitude (and thus the annual solar radiation dose in the region concerned), regional eating habits and genetic predisposition. The relationship between sun exposure and MS prevalence becomes even more apparent when examining genetically nearly homogeneous regions with similar diets. The figure shows the north-south gradient of MS prevalence in the United Kingdom. The difference between the Guersney Region and the Orkney Islands is a factor of 2.5 in the number of cases per 100,000 population over only 8 degrees of latitude north-south difference (Rosati 2001).

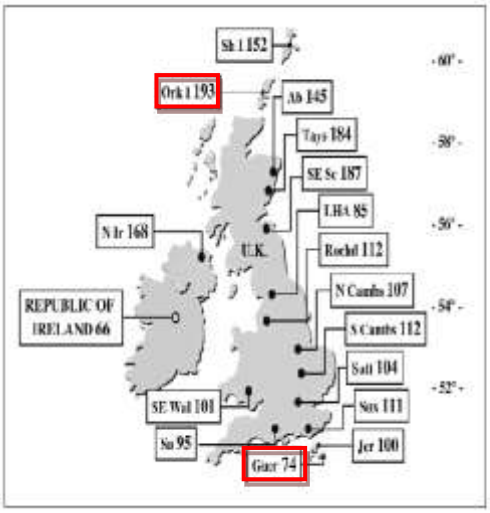


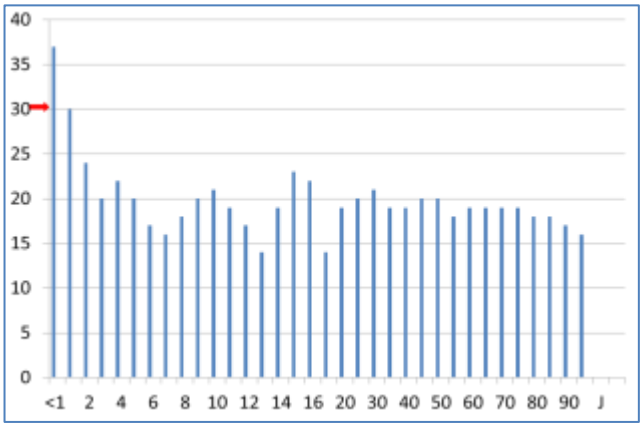
Fig. 1 Distribution of MS in the UK and the Republic of Ireland. Study area (prevalence year): *Sh I*, Shetland Islands (1974); *Ork I*, Orkney Islands (1985); *Ab*, Aberdeen (1980); *Tays*, Tayside (1996); *SE Sc*, South East Scotland (1995); *LHA*, Leeds Health Authority (1986); *Rochd*, Rochdale (1988); *N Cambs*; North Cambridgeshire (1995); *S Cambs*, South Cambridgeshire (1990); *Sutt*, Sutton (1985); *Sus*, Sussex (1990); *Jer*, Jersey (1991); *Guer*, Guernsey (1991); *So*, Southampton (1987); *SE Wal*, South East Wales (1985); *N Ir*, Northern Ireland (1996); Republic of Ireland (1971)

However, this pronounced geographically oriented epidemiological aspect in the development of MS cannot be upheld like this any longer. This is because of increasing life style changes occurring parallel to the growing industrialization, independently of latitude. The comparison of two studies involving White nurses in the United States clearly demonstrates this. The first study, which was carried out at the beginning of the last century, showed that participants from the Northern states were approximately three times more likely to suffer from MS than participants from Southern states. In the second study, which was conducted in the second half of the last century, no significant difference was found in the incidence of multiple sclerosis between the Northern and Southern states in this population (Ascherio 2013).

Even more impressive are publicized findings from Iran, whose capital Tehran lays approximately on the 36. degree latitude. Its geographic location corresponds to the Southern Mediterranean countries and the Southern United States which are quite sunny regions. Alongside economic and political changes in recent decades, a dramatic increase in MS incidences was reported. In Tehran, for example, the disease incidence (Elhami 2011) increased in women by a factor of eight in less than 20 years. Similar trends were also observed in the rest of Iran, especially in big cities. Parallel to this, a widespread and pronounced vitamin D deficiency was detected in the country, particularly amongst women (concealing clothing). Clearly, life -style factors have become more crucial than latitude in determining MS prevalence (Etemadifar 2013) . This is highly relevant for considerations in the primary and secondary prevention of multiple sclerosis.

What does lack of sunlight mean ?

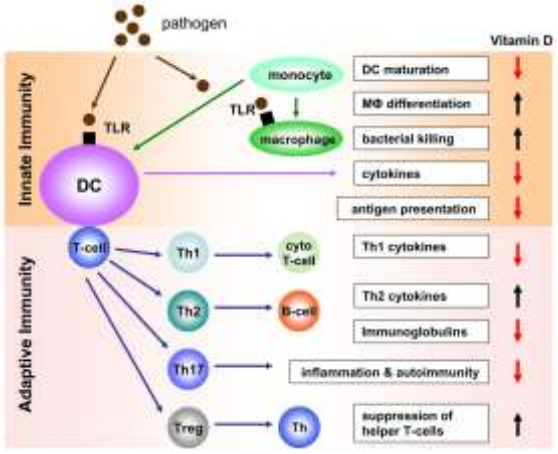
Most importantly, it means that the production of vitamin D through UVB radiation on the skin does not occur. Only a small part is fed through the food. Vitamin D is a pro-hormone, which is needed not only for bone metabolism but also for healthy functioning of literally all organs. Furthermore, up to 1000 genes are triggered by vitamin D. In Germany, a vast majority of the population irrespective of age suffer from vitamin D deficiency. This is true particularly in the winter months as demonstrated in a study involving 5000 patients from the



Rhine / Main area (Lemberg 2012). Only infants supplemented with vitamin D have normal levels over 30ng/ml. The wide impact of vitamin D on the healthy functioning of our bodies is best documented for the skeletal system but it plays a part in almost all chronic diseases, from the cardiovascular system to cancers and almost always involving the immune system. The latter is discussed further down in more detail.

In addition, the sun influences various metabolic processes. It is worth noting its role in triggering the formation of serotonin (also called happiness hormone) in the brain. Serotonin not only plays an important part in depression, it also stimulates the formation of new nerve cells in the brain. Another area is the not much researched formation of Urocanic acid, which is also formed under the influence of UV radiation from histidine (non essential amino acid) in the epidermis. Urocanic acid has a direct influence on the formation of T cells and protective immunomodulatory properties (Correale 2013)..

Vitamin D and the immune system



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Lately, a number of findings were published showing that vitamin D also played an important role in the pathophysiology of autoimmune diseases. This observation was particularly supported by experimental studies demonstrating that vitamin D is instrumental in regulating the production of chemokines, counteracting inflammation in autoimmune diseases and facilitating the differentiation of immune cells so that tolerance to its own tissue is increased. Chemokines are a group of signaling proteins which regulate the attraction of immune cells to the site of inflammation (see figure, Hewison 2010). The risk of severe or very severe vitamin D deficiency is particularly high in patients with MS. A Dutch study involving a few hundred MS patients (Smolders 2008) reported an average vitamin D blood level of just below 20 ng / ml and clearly showed that degree of disability (EDSS) was closely correlated to vitamin D status..

Consequences for the treatment of MS

A targeted therapy of MS with vitamin D has long been discussed (Smolders, 2012). The basis for this consideration was a clinical study in which MS patients experiencing a clinical relapse were administered high doses of vitamin D for a period of 28 weeks. The daily intake was 4000-40000 IU (Kimball SM 2007). The treatment was carried out without complications and complaints by the patients. This showed the wide therapeutic range and safety of vitamin D therapy. While the clinical course of the disease did not change in the short term of the treatment, the number of detectable lesions in the brain reduced by 50% during therapy! In another study, it

was shown that the probability of a relapse decreased by 12% when vitamin D level in serum was increased by 10nmol /l (Simpson 2010).

Surely not all about the role of vitamin D in MS is yet known. Still, it is evident that attention to vitamin D level in the treatment of MS is crucial. There are unused opportunities and unnecessary risks taken if the measurement and optimization of vitamin D in MS treatment is not given priority (Pierrot-D. 2013).

Furthermore it needs to be kept in mind that the influence of vitamin D on our bodies goes beyond MS. Vitamin D deficiency is associated with health problems co-morbid with MS such as high blood pressure, depression, metabolism disorders and migraine (Horton, 2010).

Concrete recommendations

For MS patients, the vitamin D serum levels should be at least between 40 and 60 ng / ml. Low levels can be increased through supplementation or monitored exposure to the sun. Regular exposure for about 10-15 minutes a day on as much unprotected skin as possible (at least arms and legs) is recommended to facilitate the above mentioned physiological effects. A Dutch study showed that depression in MS is inversely correlated with the duration of exposure to the sun whereas Vitamin D supplementation has hardly any influence (Knippenberg 2013). As a maintenance dose 4,000-5,000 IU daily (at least in the winter months) is established as a rule of thumb for 70 kg body weight. A regular check of vitamin D and calcium levels (every 3 - 6 months) is recommended.

Special Note - interferon-β and vitamin D

An important study, particularly for practitioners treating people with MS, showed that administering interferon-ß to MS patients with a distinct vitamin D deficiency can have disasterous consequences for the patient. An Australian group demonstrated that relapse rate increased by up to a factor 2 when the vitamin D blood serum level at the start of treatment with interferon-β was below 20 ng / ml. Above this level, the immunomodulatory effects of interferon β were enhanced (N Stewart et al 2012).

From today's perspective, the determination of vitamin D blood level and the elimination of deficiencies are necessary and mandatory before immunomodulatory action should be taken. This fact unfortunately only slowly finds its way into the standard neurological treatment.

In short

Vitamin D and sun have a decisive influence on the immune system

Vitamin D serum levels between 40 and 60 ng / ml are the target

Vitamin D supplementation 4000 - 5000 IU daily / Sun 10-15 min daily

Be aware of the interaction between interferon-β and vitamin D

Relevant studies

Ascherio 2013: Ascherio, Alberto (2013): Environmental factors in multiple sclerosis. In: Expert Rev Neurotherapeutics 13 (12s), S. 3–9

Correale 2013: Correale, Jorge; Farez, Mauricio F. (2013): Modulation of multiple sclerosis by sunlight exposure: Role of cis-urocanic acid. In: Journal of Neuroimmunology 261 (1-2), S. 134–140.

Elhami 2011: Elhami, Seyedeh-Robab, Mohammad, Kazem; Sahraian, Mohammad Ali; Eftekhar, Hassan (2011): A 20-Year Incidence Trend (1989–2008) and Point Prevalence (March 20, 2009) of Multiple Sclerosis in Tehran, Iran: A Population-Based Study. In: Neuroepidemiology 36 (3), S. 141–147.

Etemadifar 2013: Etemadifar, Masoud (2013): Epidemiology of Multiple Sclerosis in Iran: A Systematic Review. In: European Neurology 70, 2013, S. 356–363.

Hewison 2010: Hewison, Martin (2010): Vitamin D and the Immune System: New Perspectives on an Old Theme. In: Endocrinology & Metabolism Clinics of North America 39 (2), S. 365–379.

Horton 2010: Horton, Myles; Rudick, Richard A.; Hara-Cleaver, Claire; Marrie, Ruth Ann (2010): Validation of a Self-Report Comorbidity Questionnaire for Multiple Sclerosis. In: Neuroepidemiology 35 (2), S. 83–90.

Kimball SM 2007: Kimball SM, Ursell MR, O'Connor P, Vieth R (2007): Safety of vitamin D3 in adults with multiple sclerosis. In: American Journal of Clinical Nutrition 86 (3), S. 645–651.

Knippenberg 2013: Knippenberg, S.; Damoiseaux, J.; Bol, Y.; Hupperts, R.; Taylor, B. V.; Ponsonby, A-L et al. (2013): Higher levels of reported sun exposure, and not vitamin D status, are associated with less depressive symptoms and fatigue in multiple sclerosis. In: Acta Neurol. Scand.

Lemberg 2012: Lemberg U (2012): Untersuchung zur Epidemiologie und Therapie des Vitamin D-Mangels in Deutschland, Dissertation Med. Fakultät, Universität Mainz.

Pierrot-D.2013: Pierrot-Deseilligny, C.; Souberbielle, J.-C (2013): Contribution of vitamin D insufficiency to the pathogenesis of multiple sclerosis. In: Therapeutic Advances in Neurological Disorders.

Rosati 2001: Rosati, G. (2001): The prevalence of multiple sclerosis in the world_an update, Rosati. In: Neurol Sci (22), S. 117–139.

Simpson 2010: Simpson, Steve; Taylor, Bruce; Blizzard, Leigh; Ponsonby, Anne-Louise; Pittas, Fotini; Tremlett, Helen et al. (2010): Higher 25-hydroxyvitamin D is associated with lower relapse risk in multiple sclerosis. In: Ann. Neurol. 68 (2), S. 193–203.

Smolders 2008: Smolders J, Damoiseaux J, Menheere P, Hupperts R (2008): Vitamin D as an immune modulator in multiple sclerosis, a review. In: Journal of neuroimmunology 194 (1-2), S. 7–17.

Smolders 2012: Smolders, Joost; Hupperts, Raymond; Barkhof, Frederik; Grimaldi, Luigi M.E; Holmoy, Trygve; Killestein, Joep et al.: Efficacy of vitamin D3 as add-on therapy in patients with relapsing–remitting multiple sclerosis receiving subcutaneous interferon beta-1a: A Phase II, multicenter, double-blind, randomized, placebo-controlled trial. In: *Journal of the Neurological Sciences* 311 (1-2), S. 44–49.

Stewart N. 2012: Stewart, N.; Simpson, S.; van der Mei, I.; Ponsonby, A.-L; Blizzard, L.; Dwyer, T. et al. (2012): Interferon- and serum 25-hydroxyvitamin D interact to modulate relapse risk in MS. In: *Neurology* 79 (3), S. 254–260.

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