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Progressive multifocal leukoencephalopathy in patients using dimethylfumarate

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A male patient between 70 and 80 years was hospitalized for lisping speech, left hanging mouth, mood swings and memory impairment. Dimethylfumarate used for psoriasis, was withdrawn. Laboratory evaluation showed leukocytes of 6.5 x 10^9/L and lymphopenia grade 3 (0.42 x 10^9/L). MRI-brain showed a contrast enhancing rightsided parietotemporal lesion. Differential diagnosis included glioma, lymphoma, or opportunistic infection after dimethylfumarate. Lumbular punction showed no lymphoma or infection. Subsequent brain biopsy was positive for JC virus, confirming the diagnosis progressive multifocal leukoencephalopathy (PML). Symptoms gradually improved over weeks. PML is a severe demyelinating central nervous system disease caused by a brain infection with JC virus. JC virus infections are common, but PML occurs almost exclusively in immunocompromised individuals. In The Netherlands dimethylfumarate Psorinovo® is used as self-compounded drug for psoriasis. Dimethylfumarate Tecfidera® received registration for multiple sclerosis in The Netherlands in 2014. Several cases of dimethylfumarate associated PML were published. The bioactive metabolite monomethyl fumarate is known to have immunomodulatory effects. Hypotheses of how dimethylfumarate may induce PML, include reduction of peripheral blood lymphocytes by anti-proliferative and pro-apoptotic effects or inhibition of integrin a4 expression in circulating lymphocytes. In 2015 the European Medicines Agency (EMA) issued monitoring recommendations for dimethylfumarate Tecfidera®, including complete blood counts before and during treatment for timely detection of lymphocytopenia and a baseline MRI-brain. It is important to include PML in the differential diagnosis in patients with neurological deterioration while on therapy with dimethylfumarate, and to realize that a negative lumbar punction does not rule out PML.