A Case Report of Solitary Sclerosis: This is Really Multiple Sclerosis

Christine Lebrun · Mikael Cohen · Lydiane Mondot · Xavier Ayrignac · Pierre Labauge

Received: July 2, 2017 / Published online: August 24, 2017 © The Author(s) 2017. This article is an open access publication

ABSTRACT

Progressive solitary sclerosis is characterized by an isolated central nervous system demyelinating lesion arising in the spinal cord and brainstem, responsible for progressive motor impairment. We describe the case of a 40-year-old patient treated for more than 2 years with high doses of biotin (CERENDAY®) for progressive symptoms of solitary sclerosis, who presented asymptomatic new T2 white matter lesions on brain magnetic resonance imaging (MRI). As there is no treatment option for solitary sclerosis, high doses of biotin were proposed, but had no impact on the progression of motor deficit. As the brain MRI showed no evidence of T2 lesions during the 10 years before the introduction of biotin, the demonstration of dissemination over time with this treatment raises questions. High doses of biotin have shown efficacy in some patients with spinal progressive MS, but could reveal a latent inflammatory condition.

Keywords: Biotin; Brain MRI; Progressive MS; Solitary sclerosis

INTRODUCTION

Solitary sclerosis is a very rare entity described as a focal demyelination involving the cervicomedullary junction of the spinal cord, responsible for a progressive motor deficit [1, 2]. Prior to 2014, there was no evidence of a real impact of disease-modifying therapies on progressive forms of multiple sclerosis (MS). Treatment with orally administered high doses of biotin has recently shown efficacy in a subset of patients with a progressive spinal form of MS [3]. We report the case of a patient who underwent 2 years of treatment with high doses of biotin (CERENDAY®), followed by the appearance of asymptomatic new T2 lesions on brain MRI suggestive of MS.

CASE REPORT

In January 2000, a 40-year-old man without significant medical history presented with a...
progressive right-side disability. After 2 years of follow-up, clinical examination revealed spastic right hemiparesis and brisk reflexes in the upper and lower limbs, without other neurological abnormalities, resulting in an EDSS score of 4. An initial MRI of the brain and spinal cord was performed in 2002, with follow-up scans every 2 years thereafter. A solitary, well-delimited lesion involving the corticospinal tract was found at the level of the cervicomedullary junction (Fig. 1a). There was no mass effect and no gadolinium enhancement. Brain and spinal MRI performed 2 years later showed no evolution of this lesion and no spatial dissemination (Fig. 1b). A visual-evoked potential study was negative. CSF analysis showed a white blood cell count of 1 and normal protein level (25 mg/dl), with oligoclonal bands (OCB) and a slight increase in the IgG index: 0.77 (N < 0.7). Spasticity and motor deficit increased slowly over years, and in 2010, the EDSS score had increased to 6 and MRI features were unchanged (Fig. 1c). Brain and spinal cord MRI was performed regularly over a 15-year follow-up, with no change. As solitary sclerosis was identified as a progressive form of MS, treatment with high-dose biotin (CERENDAY®, 100 mg, three times a day) was proposed and started in 2015. After 2 years, the patient reported no improvement, and the EDSS score was unchanged. A decision was made to stop the treatment. A brain MRI performed at that time demonstrated new T2 lesions, with morphology, size and location fulfilling MS criteria (Fig. 1d). Informed consent was obtained from the patient for being included in the study.

DISCUSSION

MS diagnosis is based on the McDonald criteria (2010). A diagnosis of primary progressive MS (PP-MS) requires progressive worsening of symptoms over 1 year and two of three additional features (OCB on CSF study, at least one inflammatory lesion on brain MRI and two spinal cord lesions). However, there are patients who are now recognized as having features strongly suggesting MS diagnosis (OCB on CSF study, partial myelitis on spinal cord MRI), in the absence of the required diagnostic criteria. In 2012, Schmalstieg et al. [1] reported the first series of seven patients with solitary sclerosis sharing common features: worsening of motor symptoms over 1 year, and a single CNS demyelinating lesion of the spinal cord (cervical level or cervicomedullary junction), in the absence of other definite CNS demyelinating lesions. The entity was defined as solitary sclerosis (SS).

The concept of solitary sclerosis was confirmed in our national French study (five cases) [2, 4] and Italian group (eight cases) [5]. Since then, other case reports have emerged, and the Mayo Clinic group extended their previous results in a cohort of 30 cases [6]. Most published cases are characterized by the occurrence of progressive paraparesis, with a single spinal cord lesion in the absence of spatial dissemination, and OCB in the CSF study. In solitary sclerosis, brain MRI is normal or shows a single inflammatory lesion. The demyelinating nature of the solitary lesion was confirmed in two autopsied cases. In this most important published cohort from the Mayo Clinic, all the patients had insidiously progressive upper motor neuron weakness directly attributable to the solitary demyelinating lesion found on MRI, and none of them have shown any dissemination on brain MRI during the follow-up [6]. Half of the patients showed abnormal CSF with either OCB or elevated IgG index. Twenty-seven percent of the patients had non-specific T2-hyperintense lesions on brain MRI, none of which met dissemination-in-time MS criteria (new T2 or gadolinium-enhancing lesions) during the follow-up (median time 100 months (range 15–343 months). Our case is the first with such an extended follow-up period—17 years—showing new T2 lesions fulfilling MS criteria on brain MRI. The demonstration of brain T2 lesions suggestive of MS was made after 15 years of silent brain MRI, 1 year after treatment with high-dose biotin was introduced.

Biotin is a vitamin that acts as a coenzyme for carboxylases involved in key steps of energy metabolism and fatty acid synthesis. Acetyl-CoA carboxylase, a potentially rate-limiting enzyme in myelin synthesis, is activated by
Fig. 1 Brain (T2 FLAIR) and cervical MRI (T2 FSE) in 2002 (a), 2004 (b) and 2010 (c) showing an unchanged T2 cervical lesion of solitary MS and a normal brain MRI. February 2017 (d): known and unchanged lesion on cervical in T2-FSE-weighted sequence and on T2 FLAIR brain MRI, three T2 lesions (one in the posterior fossa and two periventricular) fulfilling MS criteria.
biotin. In 2014, preliminary data suggested that high doses of biotin might have an impact on disability and progression in progressive MS [3]. Since then, two double-blind placebo-controlled trials have been conducted in spinal and optic progressive MS with MD1003, the oral formulation of high-dose pharmaceutical-grade biotin (MedDaY Pharmaceuticals, EudraCT: 2013-002113-35). Preliminary results have shown that MD1003 achieved sustained reversal of MS-related disability in a subset of patients with progressive spinal (but not optic) MS and was well tolerated. Among the few serious adverse events reported in more than one patient, MS relapse occurred in five (4.9%) MD1003-treated patients and four (7.8%) placebo-treated patients, and during the extension phase, MS relapse occurred in seven of the 91 (7.7%) patients who initially received MD1003 and in two of the 42 (4.8%) patients who initially received placebo. No data have yet been published regarding MRI evolution. To date, high-dose biotin (CERENDAY®) is prescribed in France for patients with progressive MS, and requires a hospital prescription and a specific procedure, while European authorities have not labeled it, and another phase III is ongoing (NCT02936037). This restricted prescription is allowed only for patients who have not experienced clinical relapse in at least 1 year, and the potential of this new option raises new questions.

In rare cases, with a very long-term evolution, a progressive worsening of motor deficit characterizing clinical evolution of solitary MS has been observed. In these patients, as in ours, brain MRI remains unchanged. No treatment has demonstrated efficacy in halting or delaying neurological deficit. Here we report a very long-term follow-up of a patient with disease characteristics fulfilling the criteria for solitary MS, and appearance of MS lesions on further brain MR examination. Our patient did not suffer clinical deterioration and has stopped the treatment. The introduction of high-dose biotin may be involved in the occurrence of brain lesions, and imputability has to be questioned, as no cases of solitary sclerosis with dissemination in time on brain MRI have been published.

CONCLUSION

This case highlights two important points: (1) Solitary MS is a focal progressive form of MS, but does not strictly conform to the definition of primary progressive MS. Our report is the first to confirm that solitary MS is a clustered form, with the possibility of evolving to MS with dissemination-in-time and brain T2 lesions fulfilling spatial criteria. (2) Cautious MRI monitoring may be recommended for patients with progressive MS treated with high doses of biotin, in order to detect new T2- or gadolinium-enhancing lesions.

AUTHORSHIP

No funding or sponsorship was received for this study or publication of this article. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

Disclosures. Christine Lebrun has received honoraria for serving on scientific advisory boards or speakers’ fees from Biogen, Roche, Genzyme, Merck and MedDay. Lydiane Mondot, Mikael Cohen and Pierre Labauge have nothing to disclose. Xavier Ayrignac has received travel fees and honoraria from Biogen, Genzyme, Merck and Roche.

Compliance with Ethics Guidelines. Informed consent was obtained from the patient for being included in the study.

Open Access. This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (http://creativecommons.org/licenses/by-nc/4.0/), which permits any noncommercial use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.
REFERENCES

1. Schmalstieg WF, Keegan BM, Weinshenker BG. Solitary sclerosis: progressive myelopathy from solitary demyelinating lesion. Neurology. 2012;78(8):540–4. doi:10.1212/WNL.0b013e318247cc8c.

2. Cohen M, Lebrun C, Ayrignac X, Labauge P, Assouad R. Solitary sclerosis: experience from three French tertiary care centres. Mult Scler. 2015;21(9):1216. doi:10.1177/1352458515570405.

3. Tourbah A, Lebrun-Frenay C, Edan G, Clanet M, Papeix C, Vukusic S, De Séze J, MS-SPI study group, et al. MD1003 (high-dose biotin) for the treatment of progressive multiple sclerosis: a randomised, double-blind, placebo-controlled study. Mult Scler. 2016;22(13):1719–31.

4. Ayrignac X, Carra-Dalliere C, Homeyer P, Labauge P. Solitary sclerosis: progressive myelopathy from solitary demyelinating lesion. A new entity? Acta Neurol Belg. 2013;113(4):533–4. doi:10.1007/s13760-013-0182-x.

5. Lattanzi S, Logullo F, Di Bella P, Silvestrini M, Provinciali L. Multiple sclerosis, solitary sclerosis or something else. Mult Scler. 2014;20:1819–24.

6. Keegan BM, Kaufmann TJ, Weinshenker BG, Kantarci OH, Schmalstieg WF, Paz Soldan MM, Flanagan EP. Progressive solitary sclerosis: gradual motor impairment from a single CNS demyelinating lesion. Neurology. 2016;87(16):1713–9. doi:10.1212/WNL.0000000000003235.