Double seronegative longitudinally extensive transverse myelitis : preliminary study on 23 patients - M2N Study

P 296

Elisabeth Maillart[1], Françoise Durand-Dubief[2], Nicolas Collongues[3], Philippe Kerschen[4], Romain Deschamps[5], Romain Marignier[2] on behalf of the OFSEP and NOMADMUS study groups.

1.Neurology Department, Pitié-Salpêtrière Hospital, APHP, Paris, France - 2. Service de Sclérose en Plaques, Pathologies de la Myéline et Neuro-Inflammation, Hôpital Neurologique, GHE, Lyon-Bron, France - 3. Department of Neurology and Clinical investigation Center, Strasbourg University Hospital, Strasbourg, France - 4. Neurology Department, Luxembourg Hospital, Luxembourg-Ville, Luxembourg - 5.Neurology Department, Fondation A de Rothschild, Paris, France.

Background

Longitudinally extensive transverse myelitis (LETM) is frequently associated to neuromyelitis optica (NMO) spectrum disorders. However, some patients, despite a large work-up, remains negative for any diagnosis, including AQP4 and MOG auto-antibodies (Ab). For these double seronegative LETM patients, NMO criteria[1] are not fulfilled, and data about natural history and therapeutic recommendations are lacking.

Objectives

To describe clinical, biological and radiological course of patients who experienced a first episode of double seronegative LETM.

Methods

We included patients for whom, despite a comprehensive work-up including MOG-Ab and AQP4-Ab, the final diagnosis was double seronegative LETM with brain MRI at admission not suggestive of multiple sclerosis (MS). The initial work-up including CSF analysis, standard biological blood analysis, immune, viral and bacteriological assessment, was collected. Results of full body-scan and salivary gland biopsy were also collected.

Minimum clinical follow-up required was 1 year. Clinical and radiological outcomes were assessed by EDSS, brain and spinal cord MRI at 6/12/18/24 months, when available, and at last visit (last follow-up, FU).

Results

23 patients fulfilled inclusion criteria (Table1) : 13 women/10 men. Mean age at onset was 40.8 years (range 21.4-80). Mean EDSS at onset was 5.3 (range : 1-8). LETM locations are detailed in Table 1. All patients had normal or non-MS brain MRI (100%). Complete work-up was negative. All patients received an initial treatment (IV methylprednisolone, plasmapheresis or IV immunoglobulins, table 2).

Table 1 : Patients characteristics of the whole cohort

N	23	
population		
sex: F (n, %)	13	57%
age at LETM onset (median, y-range)	40,8	21,4 - 80
EDSS at LETM onset (mean- range)	5,3	1 - 8
spinal MRI during LETM episode		
• thoracic	9	39%
• cervicothoracic	7	30%
• cervical	3	13%
• whole spine	3	13%
• thoracic lumbar	1	4%
• number of vertebral segments (mean, range)	6	3 - 16
CSF analysis at LETM onset		
white cells count (/mm³, mean, range)	56	1 - 500
protein (g/L, mean, range)	0,74	0,27-2,4
intrathecal synthesis (n, %)	4	17%

Table 2 : LETM initial treatment

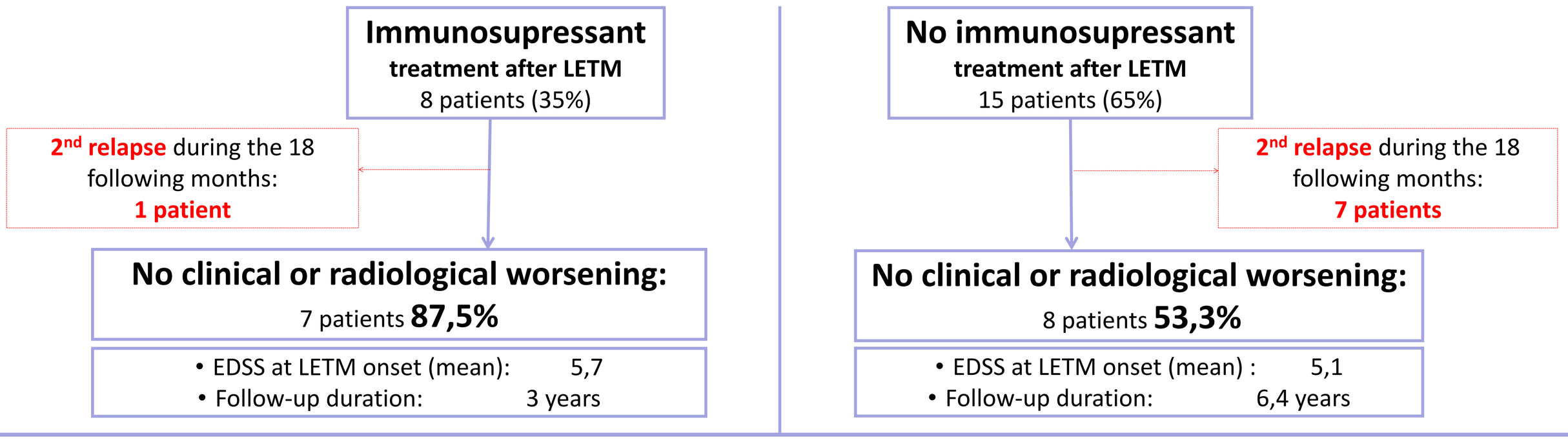
N	**23**	
Delay of treatment onset (mean, d)	16	*1-87*
first line of treatment		
• IV methylprednisolone (n)	23	**100%**
• Then oral steroids	12	52%
second line of treatment		
• n	10	**43%**
• plasmapheresis (n)	7	
• IV methylprednisolone (n)	2	
• IV immunoglobulins	1	
third line of treatment		
• n	2	**9%**
• IV methylprednisolone (n)	1	
• IV immunoglobulins	1	

Mean follow-up was 5.3 years (range 1-12). Improvement at 6 months was reported for 13 patients (62%), with however a mean EDSS at 6 and 12 months at 4.3 and 4.0, respectively (Table 3).

Table 3 : Clinical outcomes

	M0	M6	M12	M18	M24	Last FU
n	23	21	18	16	20	23
Improved patients (%)	-	62%	67%	69%	70%	**74%**
EDSS (mean)	**5,3**	4,3	4	4,6	4	**3,5**
range	1 - 8	0 - 8	0 - 8	1 - 8	1 - 8	1 - 8

Figure 2 : Outcomes according to the therapeutic strategy



Discussion and conclusion

Considering idiopathic LETM without AQP4 and MOG-Ab, data in literature are limited.

23 cases of LETM were retrospectively studied in 2013, without the knowledge of MOG-Ab status[2]: half of the patients recovered with minimal disability (EDSS <2.5), and 30% of the patients had relapses. Another work on 56 patients with seronegative AQP4-Ab LETM highlighted that double seronegative patients had a worse outcome despite a lower risk of relapses than MOG-Ab patients[3]. In our French cohort, the majority of patients experienced incomplete recovery after a first episode of LETM. In addition, the high rate of relapse in the first year suggests a more frequently chronic relapsing course than expected. **Thus, immunosuppressive treatments should be considered after a first episode of a double seronegative LETM.**

REFERENCES

1. Wingerchuk DM, Banwell B, Bennett JL, et al. *International consensus diagnostic criteria for neuromyelitis optica spectrum disorders.* Neurology. 2015 Jul 14;85(2):177-89.
2. Sepúlveda M, Blanco Y, Rovira A, et al *Analysis of prognostic factors associated with longitudinally extensive transverse myelitis*. Mult Scler. 2013 May;19(6):742-8.
3. Álvaro Cobo-Calvo, María Sepúlveda, et al. *Antibodies to myelin oligodendrocyte glycoprotein in aquaporin 4 antibody seronegative longitudinally extensive transverse myelitis: Clinical and prognostic implications*. Mult Scler J. 2016; 22(3):312-9.

This work has been supported by a grant provided by the French State and handled by the **"Agence Nationale de la Recherche"**, within the framework of the "**Investments for the Future"** programme, under the reference **ANR-10-COHO-002 Observatoire Français de la Sclérose en plaques (OFSEP**). It also received support from the **ARSEP Foundation** and the **Eugène Devic EDMUS Foundation against multiple sclerosis.**

Disclosures : E Maillart has received consulting and lecturing fees, travel grants from Biogen, Genzyme, Novartis, Merck Serono, Roche and Teva Pharma and research support from Novartis. F Durand-Dubief has received consulting and lecturing fees, travel grants and research support from Biogen, Genzyme, Novartis, Merck Serono, Roche, Sanofi Aventis and Teva Pharma. N Collongues has received consulting and lecturing fees, travel grants and research support from Biogen, Genentech, Genzyme, Novartis, Meday, Merck Serono, Roche, Sanofi Aventis and Teva Pharma. P Kerschen and R Deschamps have nothing to disclose. R Marignier has received consulting and lecturing fees, travel grants and research support from Biogen, Genentech, Genzyme, Novartis, Meday, Merck Serono, Roche, Sanofi Aventis and Teva Pharma.