

Multifocal motor neuropathy: report of 5 cases in western Mexico

Nestor Alberto Estrada Venegas

ABSTRACT

Multifocal motor neuropathy is an entity with epidemiological, clinical and neurophysiological features. We describe a series of five patients with early asymmetrical limb weakness, progressive clinical course and nerve conduction studies showing motor conduction blocks. All patients had a good response to immunotherapy; interestingly this response had wide discrepancy. One patient had a clinical course of only 2 years with no improvement to immunotherapy and other with 12 years of evolution had a good clinical response. Neurophysiological studies showed only diagnostic implication and no change all over the time. This series suggest that multifocal motor neuropathy has consistency in its epidemiological description, with female predominant, clinical response to immunoglobulin, however this response is not conditioned to time between symptom beginning and time of diagnosis.

Key words: multifocal motor neuropathy, immunotherapy, clinical response

Neuropatía motora multifocal: reporte de 5 casos en el oeste de México

RESUMEN

Neuropatía motora multifocal es una entidad con características epidemiológicas, clínicas y neurofisiológicas. Describimos una serie de cinco pacientes con principios de debilidad en las extremidades asimétricas, curso clínico progresivo y estudios de conducción nerviosa que muestra bloqueos de conducción motora. Todos los pacientes tuvieron una buena respuesta a la inmunoterapia; curiosamente esta respuesta tuvo gran discrepancia. Un paciente tuvo una evolución clínica de sólo 2 años sin mejoría a la inmunoterapia y otra con 12 años de evolución tuvo una buena respuesta clínica. Los estudios neurofisiológicos mostraron sólo una implicación de diagnóstico y ningún cambio en todo el tiempo. Esta serie sugiere que la neuropatía motora multifocal tiene consistencia en su descripción epidemiológica, con predominio femenino, la respuesta clínica a la inmunoglobulina; sin embargo, esta respuesta no está condicionada al tiempo entre los síntomas de inicio y el momento del diagnóstico.

Palabras clave: neuropatía motora multifocal, inmunoterapia, conducción nerviosa, respuesta clínica.

Multifocal motor neuropathy (MNN) is a recently defined disease just described in 1986¹. It is a rare entity with prevalence reported of less than 1 per 100,000². It's main characteristic is exclusively motor progressive, early asymmetry and absence of sensitive features³. Immunotherapy response and association with autoimmune disease and the high titers of pro inflammatory cytokines in sera of these patients have elucidated a probable immune mediated pathophysiology^{4,5}. Clinical features such as asymmetrical pattern, progressive course, absence of

sensory abnormalities and it's typical nerve blockade have been taken into account for the definition of criteria for its diagnosis and treatment. A specific marker with high sensitivity and specificity has not been found yet therefore the clinical pattern remains as the main feature for the diagnosis.

Recibido: XXXXX Aceptado: XXXXX

Resident Department of Neurology, National Medical Center of Western, Mexican Institute of Social Security, Guadalajara, Jalisco, Mexico.

Cases

We report 5 patients with history of progressive limb disability, no sensitive involvement and asymmetry findings. The average age was 58 with a standard deviation of 18 years.

Table 1. Patients' characteristics.

Patient	Age	Time of symptoms	Firts Sympton	Comorbility	DSPi	DSAI	NB
1	50	2	Distal upper bilateral weakness	Hypertension	8	6	yes
2	76	12	Proximal lower limb weakness	None	4	5	yes
3	52	4	Distal Left lower limb weakness	None	4	3	yes
4	79	10	Proximal left lower limb weakness	Hypertension	3	4	yes
5	37	2	Distal right lower limb weakness	None	3	2	yes

DSPi: disability score previous immunoglobulin. DSAI: disability score after immunoglobulin. NB: Nerve Blockade

An average time of evolution of 6 years was denoted. An asymmetrical course was established with the contralateral side involved in 2 years average. Myotathic reflexes were absent in all the patients and all showed fasciculations by the time they sought for medical attention. Gait assessment showed steppage in 4 patients. None developed bulbar or respiratory muscle weakness. Vibration sensitivity and implicated in only one patient. The media time between the beginning of weakness and immunotherapy was 2.6 years. The INCAT (Inflammatory Neuropathy Cause and Treatment) was used to graduate the activity limitation in these patients; measures were made before and after the immunotherapy⁶.

Nerve conduction studies showed a reduction or absence in compound muscle action potential (CMAP) area in nerves median, ulnar and peroneal in the 5 patients. Mild sensorial changes were found however without neurophysiological significance. Lumbar punction was made in all the patients without abnormalities. Neurophysiological findings persist all over the time in spite of clinical response.

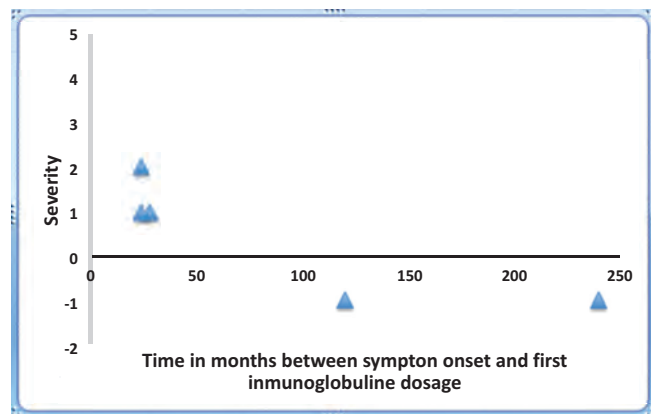


Figure 1. Comparison severity and the time between symptoms beginning the first immunoglobulin dosage

All the patients showed response to immunoglobulin, the clinical response was related inversely proportional to the time interval between symptom onset and first immunoglobulin dosage. The clinical response was particularly evident in distal strength.

DISCUSSION

Multifocal motor neuropathy is a recently described demyelinating motor asymmetric neuropathy with no sensorial abnormalities included in the spectrum of immune mediate chronic neuropathies⁷. It is the less the pattern of weakness, clinical course, absence of sensorial findings remains as the «cornerstone» for the diagnosis⁸. Recently antibodies anti ganglioside GM1 have been proposed for the supporting of the diagnosis however their sensibility is still unremarkable and not have been universally accepted in guidelines^{4,5}.

We describe 5 patients who fulfilled the clinical criteria and showed a response to immunoglobulin, taking into account by the time of the study the population of the city 1 495 182 habitants¹¹ accordingly to the literature we showed a prevalence of 0.34 cases per 100,000 Hab. Every patient complained of limb weakness with early distal upper limb involvement. A mean time of 2 years was remained for bilateral weakness. In our series female gender was more affected than male, which is against what is reported.

The isolated asymmetrical motor dysfunction is a challenge to diagnosis especially with patient with a short of the disease. Having a high insight to the development of motor neuron disease, sensorial or symmetrical symptoms at the beginning of the disease¹², however the response to immunoglobulin and the neurophysiological settings, in physical findings usually the muscle present with atrophy notwithstanding hypertrophy has been reported¹³ The five patients showed some response to immunoglobulin although this was related inversely to the time between the initial symptoms and the first immunoglobulin dosage. This response did not change the disability both as the strength according to trials; clinical response was predominant in the distal muscles¹⁴. However besides time there is no clinical Although an association with immune mediated diseases has been described¹⁵ we did not find any hint of autoimmunity in neither the patients nor the family history, though the frequency of autoimmune diseases is increased in patients with multifocal motor neuropathy.

The pathophysiology of MMN is not totally elucidated, the main question is to determine how a demyelinating disease can lead to nerve blockade and

the reason of the vulnerability of some points to this. What we already know relies on the propriety of nodal segment of motor axon more than the structural properties of ganglioside, specially GM1, which density does not differ between sensitive and motor axons¹⁶ and this may be the explanation for the absence of absolute specificity for anti-GM1 antibodies, therefore its presence may suggest it but not be the gold standard^{17,18}. For instance these antibodies may be found in other lower motor neuron diseases¹⁹. Then the pathophysiology of nerve blockade may be related to the biophysical properties of motor axons, thus the demyelinating process may lead to decrease in strength-duration time constant (the time of current that is twice the rheobase, this latter is the minimum current to produce an action potential) in motor axons with an smaller current and this lead to a decrease in the security factor which is the cause of impulse blockade. This does not really occur in sensorial axons due to the larger strength-duration time constant²⁰.

The clinical response to immunoglobulin can not be predicted based on clinical features but some association has been linked to the presence of A-waves²¹, the clinical response to immunoglobulin is conditioned mostly by clinical and electrophysiological findings thus the importance of neuron blockade demonstration²². In these cases every patient had a blockade demonstrated

This series support the validation of the clinical criteria for the diagnosis and remarks the importance of graduating the disease, for instance the mean age was 58, this represent people who according to the mean life expectative, will represent people who will necessitate at least 20 years of independency, there the importance of early diagnosis and beginning of the treatment. The clinical response may not be mediated by the grade of atrophy. One patient interestingly showed a presentation before menopause this patient has no autoimmunity but a family history of cancer; this implies a long tem careful surveillance. MMN is been linked to lymphoma, gastric and lung adenocarcinoma^{24,23}.

Important pitfalls can be concluded from this analysis. First of all the prevalence and sex predilection is according to what has been reported. Second, the immunoglobulin response improves strength but not disability and after a period of time, which has not been already established, this response to immunotherapy decreases. Third this decrease may be related to axonal damage however we observed that no matter the course of the disease we found axonal damage in every patient so this may pose the question, Is the axonal finding a stage in the natural history due to spread and chronic

demyelinating process? Or is it a more aggressive variation of the disease where we must have a lower threshold for other autoimmune mediated or even neoplastic diseases? Further research may need it.

Acknowledgements

We thank Jesus Manuel Gallegos Gonzalez MD for the facility to gather the data and metodological assistance.

REFERENCES

1. Léger J. Multifocal motor neuropathy with persistent conduction blocks: 18 years on. *Rev Neurol (Paris)*. 2004;160:889-98.
2. Miyashiro A, Matsui N, Shimatani Y, Nodera H, Izumi Y, Kuwabara S et al. Are multifocal motor neuropathy patients underdiagnosed? An epidemiological survey in Japan. *Muscle Nerve* 2014; 49: 357-61.
3. Nobile E. Multifocal motor neuropathy. *J Neuroimmunology* 2001;115:4-18.
4. Londono X, Lewis R. Multifocal Motor Neuropathy. En Handbook of clinical neurology 3rd series. *United States of America. Elsevier* 2013:429-31.
5. Furukawa T, Matsui N, Fujita K, Miyashiro A, Nodera H, Izumi Y et al Increased proinflammatory cytokines in sera of patients with multifocal motor neuropathy. *J Neurol Sci* 2014;346:75-79.
6. Breiner A, Barnett C, Vera B. INCAT disability score: a critical analysis of its measurement properties. *Muscle & Nerve* 2014;50:164-9.
7. Lawson V, Arnold D. Multifocal motor neuropathy: a review of pathogenesis, diagnosis, and treatment. *Neuropsychiatric Disease and Treatment* 2014; 10:567-76.
8. Nobile-Orazio E, Giannotta C, Musset L, Messina P, Léger J. Sensitivity and predictive value of anti GM1/galactocerebroside IgM antibodies in multifocal motor neuropathy. *J Neurol Neurosurg Psychiatry* 2014; 85: 754-8.
9. European Federation of Neurological Societies/Peripheral Nerve Society Guideline(on management of multifocal motor neuropathy. Report of a joint task force of the european federation of neurological societies and the peripheral nerve Society -first revision-. *Journal of The Peripheral Nervous System* 2010;15:295-301.
10. Meuth S, Kleinschnitz C. Multifocal motor neuropathy: update on clinical characteristics, pathophysiological concepts and therapeutic options. *Eur Neurol* 2010;63:193-204.
11. Censo de población. Guadalajara, Jalisco Instituto nacional de estadística y geografía. Censo de población 2010.
12. Eldar AH, Chapman J. Guillain Barre syndrome and other immune mediated neuropathies: diagnosis and classification. *Autoimmun Rev* 2014;13:525-30.
13. Geevasinga N, Day B, Ng K. Multifocal motor neuropathy with muscle hypertrophy. *Interna Med J* 2013; 43:1237-9.
14. Hahn A, Bevdoun S, Lawson V, Oh M, Empson V, Leibi H, et al. A controlled trial of intravenous immunoglobulin in multifocal motor neuropathy. *J Peripher Nerv Syst* 2013;18:321-30.
15. Lotte V, Leonard H, Van den B, Cats E, Sanne P, Van der Pol L. Immune pathogenesis and treatment of multifocal motor neuropathy. *J Clin Immunol* 2013; 33:S38-S42.
16. Svennerholm L, Boström K, Fredman P, Jungbjer B, Lekman A, Mansson J, et al. Gangliosides and allied glycosphingolipids

- in human peripheral nerve and spinal cord. *Biochimica et biophysica Acta* 1994;1214:115-123.
17. Adams D, Kuntzer T, Burger D, Chofflon M, Magistris M, Regli F et al. Predictive value of anti-GM1 ganglioside antibodies in neuromuscular diseases: a study of 180 sera. *J Neuroimmunol* 1991;32:223-30.
 18. Van Asseldonk AT, Franssen H, Van den Berg-Vos R, Wokke J, Van den Berg L. Multifocal motor neuropathy. *Lancet Neurol* 2005;4:309-319.
 19. Niebroj-Bodosz I, Janik P, Kwiecinski H. Serum igM anti-GM1 ganglioside antibodies in lower motor neuron syndromes. *Eur J Neurol* 2000;11:13-6.
 20. Franseen H, Straver D. Pathophysiology of immune-mediated demyelinating neuropathies-part II: neurology. *Muscle Nerve* 2014;49:4-20.
 21. Dale J, Rajwinder N, Voustianiouk A, Seidel G, Panchal J, et al. Do A-waves help predict intravenous immunoglobulin response in multifocal motor neuropathy without block?
 22. Simon NG, Gretchen A, Lomen-Hoerth C. Is IV therapy warranted in progressive lower motor neuron syndromes without conduction block?. *Neurology* 2013;10;81:2116-20.
 23. Rigamonti A, Lauria G, Stanzani L, Piamarta F, Agostoni E. A case of multifocal motor neuropathy with conduction block associated with gastric and lung adenocarcinoma.
 24. Stern B, Baehring J, Kleopa K, Hochberg F. Multifocal motor neuropathy with conduction block associated with metastatic lymphoma of the nervous system. *J Neuro-oncology* 2006;78:81-4.