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Original Research Article

Recurrent Isolated optic Neuritis as Revealing form of Neuromyelitis optica spectrum disorders: Think to test twice Aquaporin 4-specific IgG

*Youssouf Benmoh[1], Mohamed Ajamat[1], Mohamed Hamid[1], Ayoub Bekkal[1], Amal Satte[2], Ahmed Bourazza[1]

[1]Department of Neurology, Mohamed V Military Teaching Hospital, Mohamed V University, Rabat, Morocco.
[2]Department of Neurophysiology, Mohamed V University, Rabat, Morocco.

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Corresponding author: Youssouf Benmoh
Department of Neurology, Mohamed V Military Teaching Hospital, Mohamed V University, Rabat, Morocco.
Email: YOUSSOUF1680@GMAIL.COM
Telephone number: 00212675619652

Abstract

Background:
Neuromyelitis optica spectrum disorders (NMOSD) is defined as a group of central nervous system (CNS) auto-immune demyelinating disease. Recently, the discovery of aquaporin 4 antibody (AQP4-IgG) increased the pathogenesis understanding, and leaded to establish new NMOSD diagnostic criteria. We report an interesting case of recurrent isolated optic neuritis with initial negative AQP4-IgG and final NMO diagnosis.

Case-report:
49 years old woman, previously healthy, presented a first neurologic episode made of acute unilateral optic neuritis with altitudinal hemi-anopsia. Cerebral MRI and cerebro-spinal fluid study went normal, as much as large immunologic, infectious and metabolic tests. As MOG-antibody and AQP4-IgG tested by indirect immunofluorescence went negative, she was treated as idiopathic optic neuritis with high-dose corticosteroids. One year after recovery, she presented the second episode of acute unilateral optic neuritis. Paraclinical tests were normal. The AQP4-IgG retested by IFI in serum went positive with high titers. The course was favorable under high-dose corticosteroids and azathioprine. She had no relapses with a follow-up of 3 years.

Conclusion:
Cell based assay had superior sensitivity than other technique detecting AQP4-IgG, with similar specificity (100%). Therefore, we can conclude that the optimal timing to detect AQP4-IgG is during the clinical attack, by cell based assays, and before any immunosuppressant therapy (plasmapheresis, Rituximab or high-dose corticosteroids). These considerations lead to better therapeutic attitude, preventing severe relapses.

Keywords: *Neuromyelitis optica spectrum disorders, Aquaporin 4 antibody, optic neuritis, multiple sclerosis.*

INTRODUCTION:

Neuromyelitis optica spectrum disorders (NMOSD) is defined as a group of central nervous system (CNS) auto-immune demyelinating disease. It was initially described by Eugene Devic in 1895 as a novel syndrome including bilateral optic neuritis and transverse myelitis [1]. Thereafter, it was described as a monophasic severe form of multiple sclerosis (MS), with negation of possible association to other systemic disease (Lupus, Goujerot-Sjogren). The discovery of new specific pathogenic biomarker has radically changed the concept of Devic's disease into larger spectrum of neurologic disorders distinguished from MS ones; named Neuormyeliti optica (NMO) spectrum disorders (SD). Today, NMOSD is defined as a relapsing disease affecting tissues beyond optic nerve and spinal cord [2], with associated specific NMO-IgG targeting astrocytic water channel aquaporin 4. We report an interesting case of recurrent isolated optic neuritis with initial negative AQP4-IgG and final NMO diagnosis.

CASE REPORT:

49 years old woman, right handed, with no previous medical history, was initially admitted for rapidly progressive visual loss. The patient presented, 7 days before her admission, acute unilateral visual loss associated to eyeball pain. There was no associated neurologic sign (headache, vomiting, nausea, weakness, dizziness or seizure), as much as no extra neurologic symptoms (cutaneous, digestive, cardiac, rheumatologic or respiratory). Visual acuity evaluation found visual loss in the right eye quoted to 8/10 and normal acuity in the left one. Visual field study found right altitudinal hemi-anopsia [Figure.1.]. On the Visual evoked potential study, P100 wave latency was elongated in right eye, time that all parameters were normal in the left one. The clinical and electro-physiologic presentation was acute optic neuritis. Thus, cerebral MRI were performed, and showed no abnormality. Cerebrospinal fluid study was normal with no intrathecal IgG synthesis and no oligoclonal bands. There was no biologic inflammatory syndrome. Immunologic test for anti DNA and anti nuclear antibodies went negative. Several infectious serologies were performed (EBV, CMV, Herpes, hepatitis B and C, VIH, tuberculosis, syphilis) and went all negative. The salivary gland biopsy was normal. The AQP4-IgG study by indirect immunofluorescence was negative, with same result for MOG-IgG study. We conclude to idiopathic optic neuritis. The patient was treated with methylprednisolone bolus (1g/d for 3 days), relayed by oral prednisone (1mg/Kg/d for 6 weeks than progressive digression to 10mg/d than withdrawal). The clinical course was favorable with recovery of normal visual acuity. One year later, she presented same visual episode, with rapidly progressive visual loss affecting the right eye. Para-clinic studies found similar results as the first episode, but with deepest right visual loss quoted to 6/10. The electro-clinic presentation was acute recurrent optic neuritis. Cerebral MRI and CSF study went normal. Larger immunologic and infectious tests were performed and went negative. Right before administration of novel methylprednisolone bolus, the AQP4-IgG were retested by indirect immunofluorescence, and went positive with high titers. The maintenance treatment was based on oral prednisone associated to azathioprine (3mg/Kg/j). The optic course was favorable with no recurrent neurologic episode with 3 years follow-up.

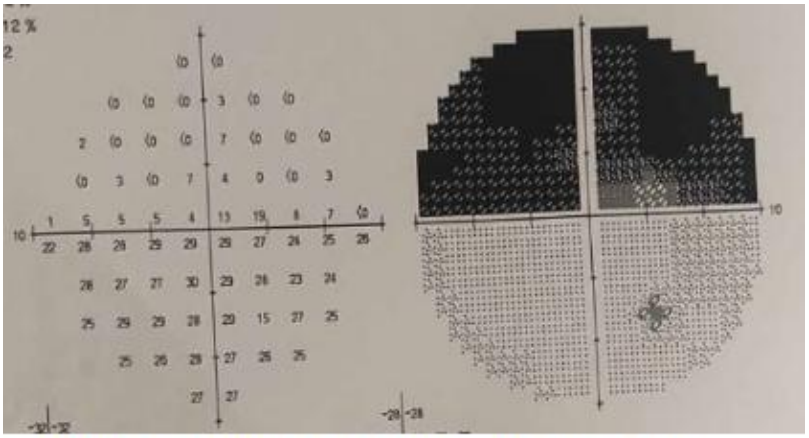

FIGURE.1. Visuel Field Study showing right altitudinal hemi-anopsia.

DISCUSSION:

NMO prevalence is above 0.3 to 4.4 per 100,000, with an incidence varying from 0.053 to 0.4 per 100,000 people and a sex ratio female/male ranging from 3:1 to 9:1 [3]. The median age is 39 years, and asian and African-american population are disproportionally affected [3; 4]. Several clinical symptoms are suggesting NMOSD: uni/bilateral optic neuritis, altitudinal hemi-anopsia, narcolepsy, insomnia, endocrinopathies, area postrema syndrome (nausea, vomiting and hiccup), symmetric paraparesis, tonic painful spasm, neuropathic pruritus [2; 5]. In 85% of NMOSD cases, patients had a relapsing course, while only 15% of cases had a monophasic illness (Devic's disease) [2; 5]. Spine, cerebral and optic nerve neuroimaging had special findings distinguished from multiple sclerosis (MS) ones. Spine lesions may be cervical or thoracic, more central and longitudinally extensive to more than 3 vertebral bodies [2]. Optic nerve MRI abnormalities are more posterior with enhancement of the chiasma [6;7]. Cerebral MRI typical aspect are localized in the astroglial foot processing in subpial and subependymal zones around lateral, third and fourth ventricles. These localizations follow the AQP4-enriched regions [8]. In contrast with MS, CSF study in NMOSD show pleocytosis more to neutrophils and eosinophils, with elevated protein and infrequently oligoclonal immunoglobulin bands [9]. Recently, the discovery of aquaporin 4 antibody increased the pathogenesis understanding, and leaded to establish new NMOSD diagnostic criteria [Table.1.][10]. In the presence of AQP4-IgG, one clinical core with elimination of other differential diagnosis, are sufficient to confirm the diagnosis. In our case, the first presentation was optic neuritis, with negative AQP4-IgG and normal optic nerve MRI. These findings were not fulfilling the 2015 NMOSD criteria. The negative AQP4-IgG do not exclude NMO diagnosis, and the timing of serum sampling is crucial [11]. A multicenter blinded comparison of variable AQP4-IgG assays concluded to higher sensitivity of cell based assays with similar sensibility

(100%) [Table.2.] [12]. The seronegative status of our patient in her first episode may be due to IFI lower sensitivity. Thus, we can conclude that the optimal timing to detect AQP4-IgG, is during the clinical attack, by cell based assays, and before any immunosuppressant therapy (plasmapheresis, Rituximab or high-dose corticosteroids).

NMOSD therapy is managed with three aspects: managing the acute attack, preventing relapses with maintenance therapy, and symptomatic treatment. The acute attack could be treated by high dose corticosteroids (1st line), plasmapheresis or human immunoglobulin (2nd line) [13; 14]. Unlike MS, NMOSD did not respond to immunomodulatory therapies which may be detrimental. The maintenance treatment is primordial to reduce number and severity of relapses. It is based on immunosuppressive therapies, most commonly: Rituximab, Mycophenolate mofetil, azathioprine, but also methotrexate and cyclophosphamide [15].

Table.1. NMOSD diagnostic criteria in adult patients according to the International Panel for Neuromyelitis optica Diagnosis IPND 2015.[10]

Diagnostic criteria for NMOSD with AQP4-IgG: 1. At least 1 core clinical characteristic 2. Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended) 3. Exclusion of alternative diagnoses
Diagnostic criteria for NMOSD without AQP4-IgG or NMOSD with unknown AQP4-IgG status: 1. At least 2 core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements: a. At least 1 core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome b. Dissemination in space (2 or more different core clinical characteristics) c. Fulfillment of additional MRI requirements, as applicable 2. Negative tests for AQP4-IgG using best available detection method, or testing unavailable 3. Exclusion of alternative diagnoses
Core clinical characteristics: 1. Optic neuritis 2. Acute myelitis 3. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting 4. Acute brainstem syndrome 5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions. 6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions.
Additional MRI requirements for NMOSD without AQP4-IgG and NMOSD with unknown AQP4-IgG status: 1. Acute optic neuritis: requires brain MRI showing (a) normal findings or only nonspecific white matter lesions, OR (b) optic nerve MRI with T2-hyperintense lesion or T -weighted gadolinium- enhancing lesion extending over > 1/2 optic nerve length or involving optic chiasm 2. Acute myelitis: requires associated intramedullary MRI lesion extending over >3 contiguous Segments (LETM) OR >3 contiguous segments of focal spinal cord atrophy in patients with history compatible with acute myelitis. 3. Area postrema syndrome: requires associated dorsal medulla/area postrema lesions. 4. Acute brainstem syndrome: requires associated periependymal brainstem lesions.

Abbreviations: AQP4 = aquaporin-4; IgG = immunoglobulin G; LETM = longitudinally extensive transverse myelitis lesions; NMOSD = neuromyelitis optica spectrum disorders.

Table.2. Results for blinded study of 146 samples (60 with neuromyelitis optica spectrum disorder and 86 controls) on multiple assays with calculated sensitivities and specificities. The final column is a measure of assay accuracy (area under the receiver operator characteristic (ROG-AUG) curve of each assay) [12].

	Sensitivity	Specificity	ROC-AUC
IIF	48.3	100.0	0.742
IPA	53.3	97.7	0.755
ELISA (RSR/Kronus)	60.0	100.0	0.800
CBA (EUROIMMUN)	73.3	100.0	0.867
FACS	76.7	100.0	0.883

Abbreviation: CBA: visual fluorescence-observation cell-based assay; ELISA: enzyme-linked immunosorbent assay; FACS: quantitative flow cytometry; IIF: indirect immunofluorescence; IPA: immunoprecipitation assay.

CONCLUSION:

We learn from this case that recurrent isolated optic neuritis may be the revealing form of NMO, and that the optimal timing for detecting AQP4-IgG is during the clinic attack, rather in serum than CSF. The cell based assay is preferred to other technique, explained by its superior sensitivity. Prior immunosuppressant therapy could mask seropositivity for AQP4-IgG. These considerations lead to better therapeutic attitude, preventing severe relapses.

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None.

Competing interests

The authors declare having no conflict of interest.

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