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Source / Izvornik: **Multiple Sclerosis, 2006, 12, 670 - 673**

Journal article, Accepted version
Rad u časopisu, Završna verzija rukopisa prihvaćena za objavljivanje (postprint)

https://doi.org/10.1177/135248506070756

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:105:487784

Recurrent optic neuromyelitis with endocrinopathies: a new syndrome or just a coincidence?

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Key words: Optic neuromyelitis, endocrinopathies, transverse myelitis, optic neuritis

Running title: Recurrent optic neuromyelitis with endocrinopathies

Summary

The spectrum of optic neuromyelitis ranges from monophasic or recurrent, idiopathic forms of the disease to optic neuromyelitis associated with autoimmune disorders. A distinct form of the disease called recurrent optic neuromyelitis with endocrinopathies, characterized by spinal cord involvement (cavitations with syringomyeloid sensory disturbance), rapid evolution to blindness and paraplegia, characteristic cerebrospinal fluid findings, and association with hypothalamus-pituitary dysfunction has recently been described. The first case of optic neuromyelitis with endocrinopathies in a female Caucasian from Europe is presented, supporting the existence of this syndrome as a separate entity.

Introduction

A combination of optic neuritis (ON) and acute myelitis without involvement of the brain is usually considered to represent optic neuromyelitis (ONM), the disease that usually results in paraplegia and blindness. The diagnostic criteria for ONM distinguish the monophasic and recurrent forms of the disease.[1] In 1997, a distinct syndrome with clinical presentation of ON and acute myelitis, called recurrent optic neuromyelitis (RONM) with endocrinopathies, was first described in eight patients from French Antilles, and then in six patients from Brazil and one from China.[2-4] We describe the first European case of the syndrome in a Caucasian female unrelated to the patients described to date.

Case report

In December 2002, a 44-year-old Caucasian female with a history of hypothyroidism and transitory thrombocytopenia during pregnancy developed ON on the right eye, with good recovery after retrobulbar corticosteroid therapy. In January 2004, she was hospitalized for paraplegia, sensory loss at the 8th thoracic level, and urinary and fecal incontinence. CSF examination revealed pleocytosis of 245/3 (180 small lymphocytes, 32 neutrophils), with protein level of 53 mg/100 ml. Oligoclonal IgG bands (OCB) were present in both CSF and serum. Viral, HIV, *Borrelia burgdorferi*, fungal and syphilis CSF serology and CSF bacterial cultures were negative, and so were immunologic tests including anticardiolipin antibodies, lupus anticoagulant, antinuclear antibodies and anti-dsDNA

antibodies. MRI was not performed on that occasion. Corticosteroid therapy (a 5-day course of 1000 mg metylprednisolon, followed by dose tapering) resulted in only slight deficit improvement. Concurrently with this bout of the disease, however before corticosteroid treatment was started, the patient developed hyperphagia with weight gain (she gained 15 kilograms), and diabetes mellitus. Thyroid hormones at this point were within normal limits, and antithyroid peroxidase antibody was negative. Nine months later she developed ON of the left eye, this time with only partial recovery. In December 2004, she developed episode of acute, partial myelitis with left hemiparesis and ipsilateral temperature and pain loss in the segmental distribution of the trigeminal nerve, with contralateral temperature and pain loss on the body. Neurological examination revealed triplegia in extension, with hyperactivity of extensor reflexes and tonic extensor spasms of the left arm and lower limbs, with the legs in adduction and slight internal rotation. CSF revealed pleocytosis of 73/3 (38 small lymphocytes, 20 neutrophils and 6 eosinophils), protein 72 mg/100 ml, and IgG index of $9.8x10^3$. OCB were identical in serum and CSF, indicating that there was no intrathecal synthesis. CSF protein electroforesis and immunoelectroforesis were normal. Viral, HIV, *Borrelia burgdorferi*, fungal and syphilis CSF serology was negative again. At this point, immunologic testing revealed elevated level of anticardiolipin IgG antibodies (105 U/ml, normal value <10), with again negative lupus anticoagulant, antinuclear antibodies and anti-dsDNA antibodies. However, repeated measurement of anticardiolipin antibodies two months later was negative. Electromyoneurography was normal, and visual evoked potentials revealed wave P100 of borderline latencies with low amplitudes. On spinal cord MRI, T1 and T2 weighted images (Figure 1A) showed a cavitation extending over the first six cervical vertebrae and a high signal intensity over the 3rd and 4th thoracic vertebrae on T2

weighted images. On transverse images, an area of high signal intensity was present in left lateral and dorsal columns of the cervical spine indicating involvement of left tractus spinalis nervi trigemini and lateral spinotalamic tract (Figure 1B). Brain MRI was normal. Upon treatment with corticosteroids (a 5-day course of 1000 mg metylprednisolon, followed by dose tapering), followed by plasmapheresis, immunoglobulin (35g/5 days) and cyclophosphamide (60 mg three times daily) therapy, the neurological status was maintained stationary.

Discussion

RONM with endocrinopathies has been described as being unique to black Antillean and Afro-Brazilian women. In the literature there are reports on only two Caucasians from Brazil with this syndrome associated with diabetes mellitus or amenorrhea,[3] which makes our patient the first case of RONM with endocrinopathies described outside Brazil.
Our patient with two bouts of ON, one of acute transverse myelitis and of partial myelitis each, and absence of MRI lesions in the cerebral white matter, met the diagnostic criteria for ONM,[1] yet distinguished from ONM by several features. The first and most striking was the association with endocrinopathies including hypothyroidism, hyperphagia with obesity, and diabetes mellitus. The obesity and diabetes mellitus developed before introducing corticosteroid treatment, and these symptoms are very likely to be hypothalamic in origin. However, it is not possible to exclude the causal relationship between these two diseases, as type II diabetes can be a consequence of obesity. As well, although antithyroid peroxidase antibodies were negative, hypothyroidism was diagnosed 15 years before development of first neurological symptoms, so it is not entirely possible

to exclude an autoimmune origin of this endocrinopathy. The patient also suffered from amenorrhea, which corresponded with the second bout of the disease, but her age and negative prolactin levels made this symptom questionable. The spectrum of endocrinopathies in RONM patients (Table 1) seems to be related to hypothalamus-pituitary dysfunction, as gadolinium enhancement was observed in the pituitary of some patients from Martinique. Also, involvement of hypothalamic structures has recently been described in two patinents with ONM, one of which has Haitian heritage.[5] These authors suggested that involvement of hypothalalmus should be included in diagnostic criteria for ONM. However we feel that hypothalamic involvement should be used as one of the markers (along with clinical picture, endocrinopathies and CSF findings) which distinguish RONM with endocrinopathies from classic ONM. It has also been shown that patients with so called Asian type of MS (which in fact represents RONM) may have elevated prolactin levels, which again implicates the involvement of hypothalamus-pituitary level.[6] Although hyperphagia with obesity and amenorrhea in our patient were also suggestive of a disorder at the hypothalamus-pituitary level, brain MRI was normal. CSF findings in patients with RONM are either normal or show pleocytosis with elevated protein level and negative OCB. In our patient, a characteristic finding was the presence of up to 41% of neutrophils in the CSF (negative CSF bacterial cultures on three occasions), clearly differentiating this syndrome from MS. CSF neutrophils have been reported in 60% of patients with recurrent ONM,[1] although it does not appear to hold for all recurrent ONM series.[7] Also, our patient showed the so-called mirror pattern, i.e. identical OCB in both serum and CSF, which did not indicate intrathecal synthesis.

In patients presenting with the symptoms of either ON or transverse myelitis, immunologic testing is of paramount importance, since the association with some of

connective tissue diseases implies a different mode of treatment. ONM in the presence of anticardiolipin antibodies is an indication for anticoagulation therapy, although some authors suggest these antibodies to merely reflect polyclonal B-cell activation that is not organ specific.[8] Nevertheless, our patient did not meet the diagnostic criteria for antiphospholipid syndrome,[9] anticardiolipin antibodies were positive in only one occasion, and other characteristic antibodies for systemic lupus erythematosus and other connective tissue disorders and vasculitis (antinuclear antibodies, anti-dsDNA antibodies and lupus anticoagulant) were repeatedly negative.

In conclusion, the patient presented had several characteristics of RONM with endocrinopathies: only the optic nerves and spinal cord were affected; there were no lesions in other parts of the central or peripheral nervous system; the clinical picture showed rapid evolution to triplegia and syringomyeloid sensory dissociation; endocrine disturbances including hypothyroidism, diabetes mellitus, hyperphagia with obesity, and amenorrhea; and MRI evidence of cavitations and demyelination of the cervical and thoracic spinal cord, without brain involvement. Although more studies are needed to define this disorder as a new syndrome, this case additionally supports the observation that RONM with endocrinopathies should be differentiated from ONM.

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Table 1 Characteristics of patients with recurrent optic neuromyelitis with endocrinopathies

Sex	Ethnicity	Age at first bout	First bout	Number of bouts	Associated endocrinopathy
Female	Antillean	30	ON	3	Amenorrhea, Hypothyroidism
Female	Antillean	17	ON	7	Obesity, Amenorrhea
Female	Antillean	29	ON	4	Obesity, Amenorrhea/ Galactorrhea, Hypothyroidism
Female	Antillean	33	ON	4	Amenorrhea/ Galactorrhea,
Female	Antillean	27	ON	5	Obesity, Amenorrhea, Hypothyroidism
Female	Antillean	35	TM	4	Amenorrhea
Female	Antillean	53	ON	4	Hypothyroidism, Diabetes insipidus, Galactorrhea
Female	Antillean	28	ON	4	Amenorrhea
Female	Afro-brazilian	30	TM	4	Amenorrhea/ Galactorrhea
Female	Afro-brazilian	55	ON	13	Amenorrhea/ Galactorrhea
Female	Afro-brazilian	30	ON	2	Amenorrhea/ Galactorrhea
Female	Afro-brazilian	35	ON	8	Hypothyroidism

Female	White-brazilian	44	ON	5	Diabetes mellitus
Female	White-brazilian	26	TM	8	Amenorrhea/ Galactorrhea
Female	Chinese	32	TM	2	Amenorrhea
Female	White	44	ON	4	Obesity, Hypothyroidism, Diabetes mellitus

ON optic neuritis; TM transverse myelitis

Figure 1 Magnetic resonance imaging findings: (A) T2 weighted image of the cervical spine showing cavitation extending over the first six vertebrae; (B) T2 weighted transverse image of the cervical spine showing an area of high signal intensity in the lateral and dorsal columns.

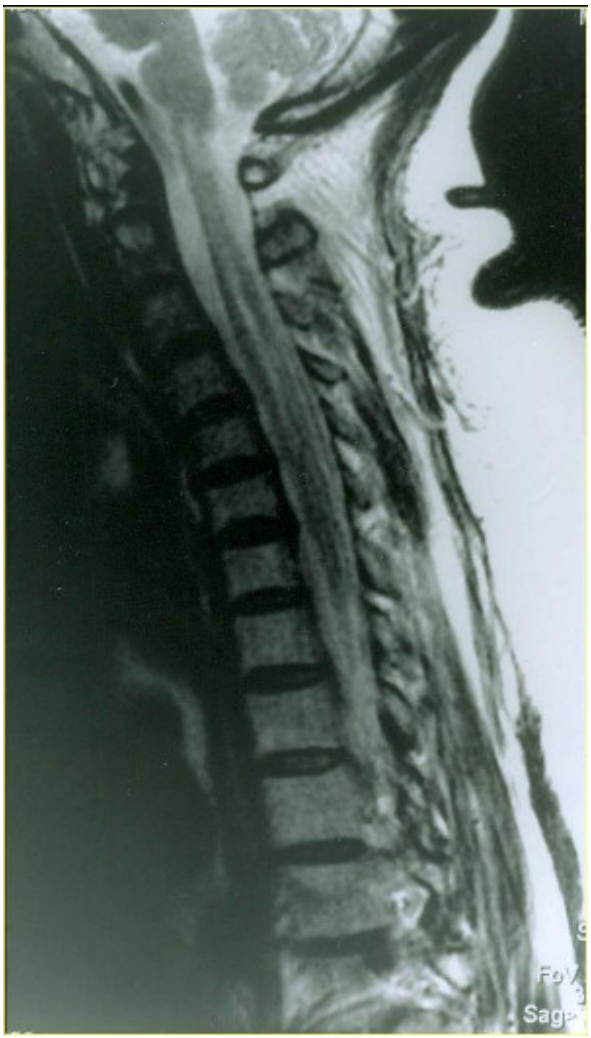

Figure 1 A

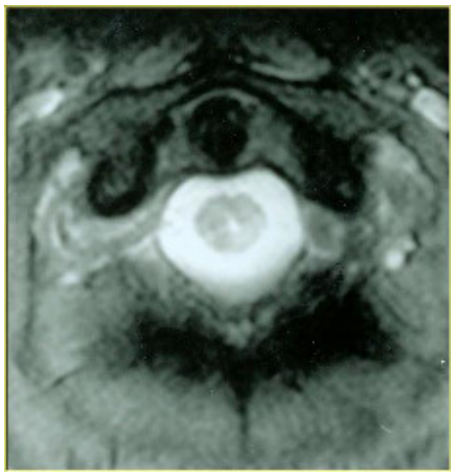

Figure 1 B