



### **Središnja medicinska knjižnica**

Zadro, I., Barun, B., Habek, M., Brinar, V. V. (2008) *Isolated cranial nerve palsies in multiple sclerosis*. Clinical Neurology and Neurosurgery, [Epub ahead of print, Corrected Proof].

<http://www.elsevier.com/locate/issn/0303-8467>

<http://dx.doi.org/10.1016/j.clineuro.2008.02.009>

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## **Isolated Cranial Nerve Palsies in Multiple Sclerosis**

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Word count: 1012

### **Authors' contributions**

Study concept and design: Zadro and Barun. Acquisition of data: Zadro, Barun, Habek, Brinar. Analysis and interpretation of data: Zadro, Barun, Habek. Drafting of the manuscript: Zadro, Barun, Habek. Critical revision of the manuscript for important intellectual content: Zadro, Barun, Habek, Brinar. Administrative, technical, and material support: Habek.

**Conflict of interest statement:** There is no conflict of interest.

## **Abstract**

Data on patients with multiple sclerosis and cranial nerve involvement as a presenting sign or a sign of disease exacerbation were retrospectively analyzed. Isolated cranial nerve involvement was present in 10.4% out of 483 patients, either as a presenting symptom (7.3%) or a symptom of disease relapse (3.1%). Trigeminal nerve was most frequently involved, followed by facial, abducens, oculomotor and cochlear nerves. Only 54% of patients had brainstem MRI lesion that could explain the symptoms. As multiple sclerosis is a disease characterized by multiple neurological symptoms, while early diagnosis and therapy are critical for the prognosis and course of the disease, the diagnosis of multiple sclerosis should be considered in young adults with cranial nerve involvement.

**Key words:** cranial nerves, multiple sclerosis, magnetic resonance imaging

## **Introduction**

Multiple sclerosis (MS) is a chronic, autoimmune, demyelinating disease of the central nervous system; however, several studies demonstrated peripheral nervous system involvement in a subgroup of patients<sup>1,2</sup>. Although brainstem involvement is common at MS onset and during the course of the disease, isolated cranial nerve involvement is rare in MS patients. However, magnetic resonance imaging (MRI) may fail to visualize every symptomatic demyelinating lesion<sup>3-5</sup>.

In this study, data on clinically isolated syndrome (CIS) and MS patients with cranial nerve involvement as a presenting sign or a sign of disease exacerbation were retrospectively analyzed.

## **Patients and Methods**

During a 5-year period (2002-2007), 483 patients admitted to our department were diagnosed as having CIS (n=120) or MS (n=363) according to McDonald's criteria<sup>6</sup>. Data on these patients were retrospectively analyzed. Brain and cervical spine MRI were performed on a 1.5 Tesla MRI device. Cerebrospinal fluid (CSF) was analyzed for cells, proteins, IgG index and oligoclonal bands; serum and CSF were tested for *Borrelia burgdorferi*, syphilis, human immunodeficiency virus (HIV), hepatitis B and C; and serum was analyzed for systemic inflammatory disease (ANA, ENA, ANCA, RF, aCL IgG, aCL IgM), sarcoidosis (ACE), vitamin B12 and folic acid deficiency, and thyroid hormones. Visual evoked potentials were also performed.

## **Results**

Fifty (10.4%) patients had signs of cranial nerve involvement, either as an initial symptom or as a symptom of MS relapse. There were 12 CIS patients and 38 MS patients (33 with RRMS and 5 with SPMS), mean age at symptom onset 30.5 (range 12-52) years. Cranial nerve palsy as a presenting sign was recorded in 35 (7.3%) patients: third nerve (n=2); fifth nerve (n=17) including trigeminal sensory neuropathy (n=9) and trigeminal neuralgia (n=8); sixth nerve (n=3); and seventh nerve (n=13) (Table 1). Cranial nerve palsy as a clinical sign of exacerbation was recorded in 15 (3.1%) patients: fifth nerve (n=6) including trigeminal sensory neuropathy in 5 and trigeminal neuralgia in one patient; sixth nerve (n=2); seventh nerve (n=5); and eighth nerve (n=2). Demyelinating brainstem lesion was found in 27 (54.0%) patients (Table 2). Study results showed third nerve involvement in 0.4%; fifth nerve involvement in 4.8% (trigeminal neuralgia in 1.9% and trigeminal sensory neuropathy in 2.9%); sixth nerve palsy in 1.0%; seventh nerve palsy in 3.7%; and eighth nerve involvement in 0.4% of the CIS and MS patients.

## **Discussion**

Although brainstem involvement is common during the course of MS, isolated cranial nerve palsies are rare. In the only study retrospectively investigating isolated cranial nerve palsy in MS, it was found in 1.6% of MS patients<sup>3</sup>. The authors conclude that isolated cranial nerve palsies more often occur as a presenting symptom than during disease relapse ( $p<0.001$ ), which is consistent with our results. However, the mentioned study did not include patients with fifth nerve involvement, which was most frequently

observed in our study patients. This may explain the difference in the rate of isolated cranial nerve involvement between these two patient cohorts.

Interestingly, the prevalence of MRI brainstem lesions in cranial nerve involvement is quite low. Thomke *et al.* report on positive brain MRI in 4 of 13 patients<sup>3</sup>. In our study, 26 of 50 patients had positive brain MRI. We compared positive MRI results between patients with cranial nerve involvement as a presenting symptom and those with cranial nerve involvement in disease relapse. We found no difference, except for patients with facial nerve involvement as a presenting symptom showing a higher rate of positive MRI findings. Both studies were performed on MRIs of 1.5 T or less, and newer MRI techniques may yield a greater percentage of positive results<sup>7</sup>.

There are only few literature reports on particular cranial nerve involvement in MS.

Three large retrospective studies investigated the causes of third nerve involvement and only 1.7% of patients were found to have MS<sup>8-10</sup>. Although described in the literature, fourth nerve involvement was not recorded in our study. This could be explained by the fact that fascicular course of the trochlear nerve is at low myelin exposure<sup>11</sup>. Truly isolated sixth nerve palsy is also rare as a presenting sign of MS, with an incidence of 1.6%<sup>4</sup>. In our study, isolated sixth nerve palsy was found in 1% of MS patients. Thomke *et al.* found 0.4% of their MS patients to have truly isolated sixth nerve palsy as a presenting sign of MS<sup>3</sup>, while Barr *et al.* report on a prevalence of 0.5%<sup>4</sup>. Other reports show MS to be responsible for 4%-9% of unilateral sixth nerve palsy in the general population<sup>8,9,12</sup>. These findings are especially important, as there is much debate in the literature on the use of MRI in patients with isolated third, fourth and sixth nerve palsies. We argue that every patient with isolated lesions of these cranial nerves should undergo

brain MRI as an initial diagnostic assessment, thus not to miss a serious pathology such as MS<sup>13</sup>.

Trigeminal neuralgia as the first manifestation of MS is reported in 0.3% and during the course of disease in 1.9% of cases<sup>14-16</sup>. Our study showed trigeminal sensory neuralgia in 1.9% of patients, either as the first sign or a relapse symptom. The pathogenetic mechanism of trigeminal sensory neuralgia in MS patients is usually caused by demyelinating lesions affecting pontine trigeminal pathways. Trigeminal sensory neuropathy secondary to MS preferentially affects the second and third division of the trigeminal nerve and was more common in our cohort than trigeminal neuralgia. Facial palsy was found as a presenting symptom in 19.6% and during the course of disease in 4.7% of Japanese patients with MS<sup>17</sup>. It was a rare symptom in our cohort, with a prevalence of 3.7%.

Eighth cranial nerve involvement is quite rare and only 0.4% of our patients suffered hearing loss as a symptom of MS. Some studies have shown that a demyelinating lesion in distal segment of the eighth cranial nerve may cause an acute hearing loss in MS<sup>18</sup>. As MS is a disease characterized by multiple neurological symptoms, while early diagnosis and therapy are critical for the prognosis and course of the disease, the diagnosis of MS should be considered in young adults with cranial nerve involvement.

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Table 1. Isolated cranial nerve palsies in multiple sclerosis (MS) patients

Cranial nerve involved	First symptom	Symptom of MS relapse	Total
III	2 (0.4%)	0 (0.0%)	2 (0.4%)
V	17 (3.5%); 9 (1.9%) TNP and 8 (1.7%) TNG	6 (1.2%); 5 (1.0%) TNP and 1 (0.2%) TNG	23 (4.7%): 14 (2.9%) TNP and 9 (1.9%) TNG
VI	3 (0.6%)	2 (0.4%)	5 (1.0%)
VII	13 (2.7%)	5 (1.0%)	18 (3.7%)
VIII	0 (0.0%)	2 (0.4%)	2 (0.4%)

TNP, trigeminal nerve neuropathy; TNG, trigeminal nerve neuralgia

Table 2. Brainstem MRI in patients with isolated cranial nerve palsies

Symptom	n	Positive brainstem MRI (n)	Negative brainstem MRI (n)
Nerve III palsy	2	1	1
Trigeminal nerve V neuropathy	14	7	7
Trigeminal nerve V neuralgia	9	4	5
Nerve VI palsy	5	2	3
Nerve VII palsy	18	12	6
Nerve VIII palsy	2	0	2