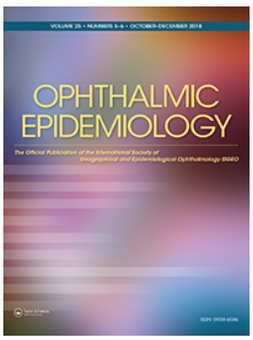

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# Incidence and Mimickers of Acute Idiopathic Optic Neuritis: Analysis of 291 Consecutive Patients from Southern Finland

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**ABSTRACT**

***Purpose***: To estimate the population-based incidence of acute idiopathic optic neuritis (ON) and analyse its differential diagnosis in patients referred with symptoms suggestive of ON.

***Methods***: Patients with suspected ON referred to the Helsinki University Hospital, serving a population of 1.5 million in Southern Finland, were reviewed between 1st May 2008 and 14th April 2012. Brain and optic nerve magnetic resonance imaging (MRI) was performed within 24 hours in 83% of patients.

***Results***: Of 291 referred patients, 184 (63%; 95% confidence interval [CI], 57–69%) were diagnosed with ON whereas 107 (37%) had another condition. The estimated crude incidence of ON in Southern Finland was 3.0 (95% CI 2.8–3.3) per 100,000 (females, 4.6 and males, 1.4). Mean age was 34 years (range 15–61), 76% were female. Two (1%) were diagnosed with neuromyelitis optica. ON as the first demyelinative episode was diagnosed in 108 (59%) patients, and MRI showed demyelinating lesions (MRI+) in 82% (95% CI, 75–89) of them. MRI+ predicted the development of multiple sclerosis (MS): 54% of MRI+ vs. 5% MRI− patients were diagnosed as MS during a mean follow-up of 7.7 years. The most common differential diagnosis was non-arteritic anterior ischemic optic neuropathy (12%). Six (2%) intracranial compressive lesions were found upon MRI scan.

***Conclusions***: More than a third of patients with symptoms suggestive of ON had another condition. Demyelinative lesions on MRI indicated higher risk of developing MS. We recommend the use of MRI to improve the differential diagnostic accuracy of ON and to identify patients with high risk of MS.

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Optic neuritis; incidence; differential diagnosis; Finland

## Introduction

Acute idiopathic optic neuritis (ON) is an inflammatory optic neuropathy that leads to subacute vision loss. It is a demyelinating disease that mostly affects young adults. The most common symptom of ON is decreased visual acuity. The diagnosis of ON is essentially clinical. No universal diagnostic criteria are available[1] and no specific treatment is known for ON. According to the Optic Neuritis Treatment Trial, intravenous high-dose corticosteroids may hasten visual recovery, but they do not improve the 6-month and 1-year outcome of visual acuity as compared to placebo.[2,3]

ON is the presenting symptom of relapsing multiple sclerosis (MS) in about 20% of cases and eventually occurs in about half of MS patients.[4–6] MS typically causes demyelination at multiple foci of the cerebrum, brainstem, or spinal cord. It presents with a wide range of signs and symptoms, including pareses of the limbs or cranial nerves, ataxia, sensory disturbances as well as autonomic nervous system (e.g. urinary incontinence) and cognitive symptoms.[7]

Another demyelinating disease that can manifest with ON is neuromyelitis optica (NMO, or Devic's disease). ON is not only a common initial symptom of NMO but also one of its main diagnostic criteria. NMO is additionally characterized by spinal symptoms from longitudinally extensive myelitis. Aquaporin-4 (AQP4) antibodies are considered an important adjunct for diagnosing NMO.[8,9] In AQP4-seropositive patients, more heterogeneous clinical symptoms are allowed in the newest diagnostic criteria.[10] NMO often leads to severely impaired mobility and reduced visual acuity or even legal blindness.[8,11] The incidence of NMO among ON patients is low in Finland[12,13] whereas the incidence and prevalence of MS are relatively high.[14–16]

Here, we followed up 291 patients with acute or subacute visual impairment suggestive of ON to identify differential diagnostic mimickers of ON, relation of

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Supplementary data for this article can be accessed here.

ON with demyelinative diseases and the value of magnetic resonance imaging (MRI) in the diagnostic and prognostic work-up.

## Materials and methods

All patients referred to the Department of Ophthalmology, Helsinki University Hospital, Finland, between 1st May 2008 and 14th April 2012 (a period of 47.5 months) with symptoms suggestive of acute or subacute ON were eligible for inclusion in this study. A subsequent diagnosis of MS was monitored during follow-up until end of 2017. Mean follow-up time was 7.7 years. The hospital receives virtually all patients with an acute ON living in its catchment area, the Hospital District of Helsinki and Uusimaa in Southern Finland. This region had a mean population of 1.53 million during our study period (28% of the population of Finland, 5.4 million in 2011). Our series is thus essentially population-based for the geographic catchment area and free of administrative selection criteria. Of 300 eligible patients,[6] 9 were excluded because of clerical errors (miscoded diagnosis or personal identification error).

For the diagnosis of ON, we adhered to some of the most common criteria: a combination of acute or subacute loss of vision, possible relative afferent pupillary defect, pain upon eye movements, and some degree of acquired colour vision deficiency. Biomicroscopic examination of the fundus was performed in all patients and indirect ophthalmoscopy in most of them. Visual fields, visual evoked potentials (VEP), and optical coherence tomography (OCT) were performed as needed to ensure the diagnosis of ON.[17]

MRI of the brain and orbits was performed within 24 hours from the admission to hospital, either with Siemens Avanto 1.5T (Siemens AG, Erlangen, Germany), Philips Achieva 3T (Philips Healthcare, Eindhoven, The Netherlands), or Siemens Verio 3T (from 2011). The MRI included T2, T2 flair, diffusion-weighted, and T1 sequences with gadolinium enhancement. MRI was not performed in 49 patients in the acute phase for various reasons: in 41 patients, MRI had been performed recently as a part of MS patient follow-up, four patients were referred immediately to a neurologist before MRI screening, and five patients had other causes (e.g. claustrophobia). A spinal MRI was obtained in all patients with spinal cord symptoms or positive or borderline AQP4 index, which we tested in all patients.[12]

## Results

During the study period, 291 patients with a condition suggestive of ON were referred; 184 (63%; 95% confidence interval [CI], 57–69) were diagnosed with ON of which 39 (21%) had optic disc swelling suggesting that most ON cases were retrobulbar. About 107 (37%) patients were eventually diagnosed with another condition (Table 1). The most common specific disease in the latter group was non-arterial ischemic optic neuropathy (NAION). It occurred in 12% of the patients and other conditions made up the remainder, including 22 with ON-like symptoms that resolved quickly (Figure 1).

### *Incidence of optic neuritis and its relation to demyelinative diseases*

The estimated crude incidence of ON in Southern Finland was 3.0 (95% CI, 2.8–3.3) per 100,000 (females, 4.6 and males, 1.4 per 100,000). The mean age was 34 years (range, 15–61 years) and 76% were female. The first ON was observed in 123 (67%) patients. Two patients (1%) with

**Table 1.** Characteristics of six patients with an intracranial expansion.

| Diagnosis | Age (years) | Sex | Symptoms at onset | Clinical findings | Treatment |
|---|---|---|---|---|---|
| Meningioma dislocating the left optic nerve | 40 | Female | VA of the left eye reduced in two weeks | VA 0.8/1.0<br>RAPD −/+, left optic disc pale | Neurosurgery |
| Meningioma compressing the right optic nerve | 40 | Female | VA of the right eye reduced in one day | VA CF/1.0<br>RAPD −/−<br>right optic disc pale | Neurosurgery |
| Meningioma with chiasmal compression | 65 | Female | VA slowly reduced in both eyes | VA 0.3/0.6<br>RAPD −/−<br>both optic discs pale | Neurosurgery |
| Intracranial aneurysm (both ophthalmic arteries) | 49 | Female | VA of the right eye reduced in one week | VA 0.1/1.0<br>RAPD ±<br>pain with eye movements | Neurosurgery |
| Intracranial aneurysm (anterior communicating artery) | 52 | Male | Four days of pain with movements of the right eye | VA 0.5/1.0<br>RAPD −/− | Refused surgery |
| Metastasis (lung cancer) | 73 | Female | VA slowly reduced in both eyes | VA 0.6/0.5. RAPD +/−<br>right optic disc swelling, paresisabducens | Palliative radiotherapy |

CF = counting fingers, VA = visual acuity, RAPD = relative afferent pupillary defect.

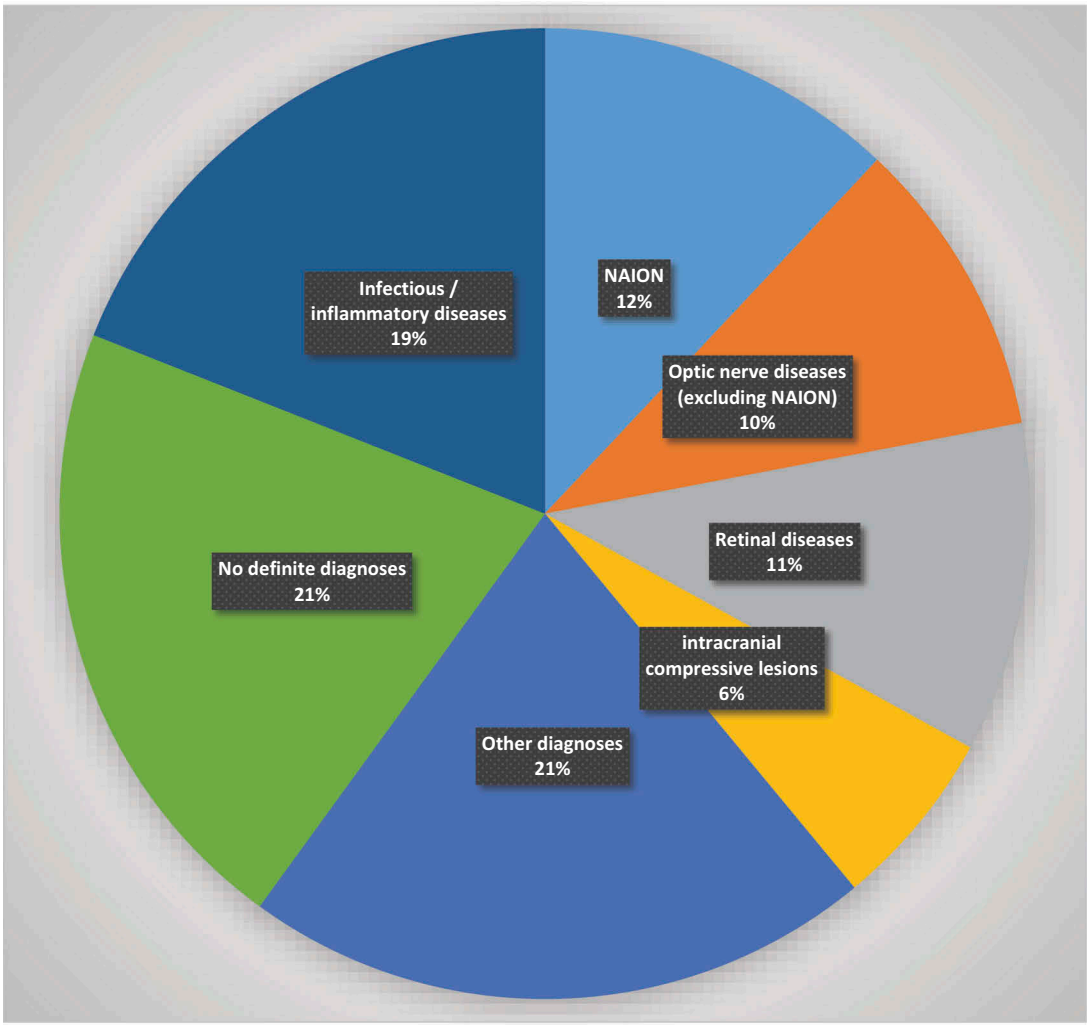


**Figure 1.** Differential diagnoses of patients with symptoms suggestive of optic neuritis at onset (n=107). Most common differential diagnose was non-arteritic ischemic optic neuropathy (NAION, 12%). 21% patients had optic neuritis-like symptoms that resolved quickly and no definite diagnosis was determined for them.

their first ON were diagnosed with NMO, and 56 patients (30%) had a previous diagnosis of MS. ON as the first demyelinative episode was diagnosed in 108 (59%) patients, and 3 (2%) patients had a recurrent ON without a diagnosis of MS.

Of the 108 patients with their first ON and without a prior diagnosis of MS, 103 were MRI screened: 84 (82%) had at least one demyelinative lesion on MRI (MRI+) and 19 (18%) did not have any lesions in MRI (MRI). Of these patients, 26 (21%) had lesions in the optic nerve only, 44 (36%) had a lesion both in the optic nerve and in the brain, and 14 (11%) in the brain only. Of the MRI+ patients with their first ON, 45 (54%) were diagnosed with MS during our follow-up (mean, 7.7 years) whereas only one (5%) of MRI− patient was diagnosed with MS: positive predictive value, 54%, negative predictive value, 94%. Three patients with recurrent ON had no previous diagnosis of MS, two of them were MRI+ and both were diagnosed with MS, while the one MRI− case did not fulfil criteria of MS during follow-up. Flow chart of the MRI findings and development of demyelinative diseases is shown in Figure 2.

### *MRI findings of non-ON patients*

Notably, 6 (2%) of the 291 patients with suspected ON had intracranial compressive lesion on MRI. These included three meningiomas, two intracranial aneurysms, and one lung cancer metastasis (Table 1).

## Discussion

Recent estimates on the incidence of acute idiopathic ON are scarce. Most data are from the time period before MRI was a common procedure, and even today in many centres the diagnosis of ON is often made without a brain MRI. With modern diagnostic means (e.g. MRI, OCT,

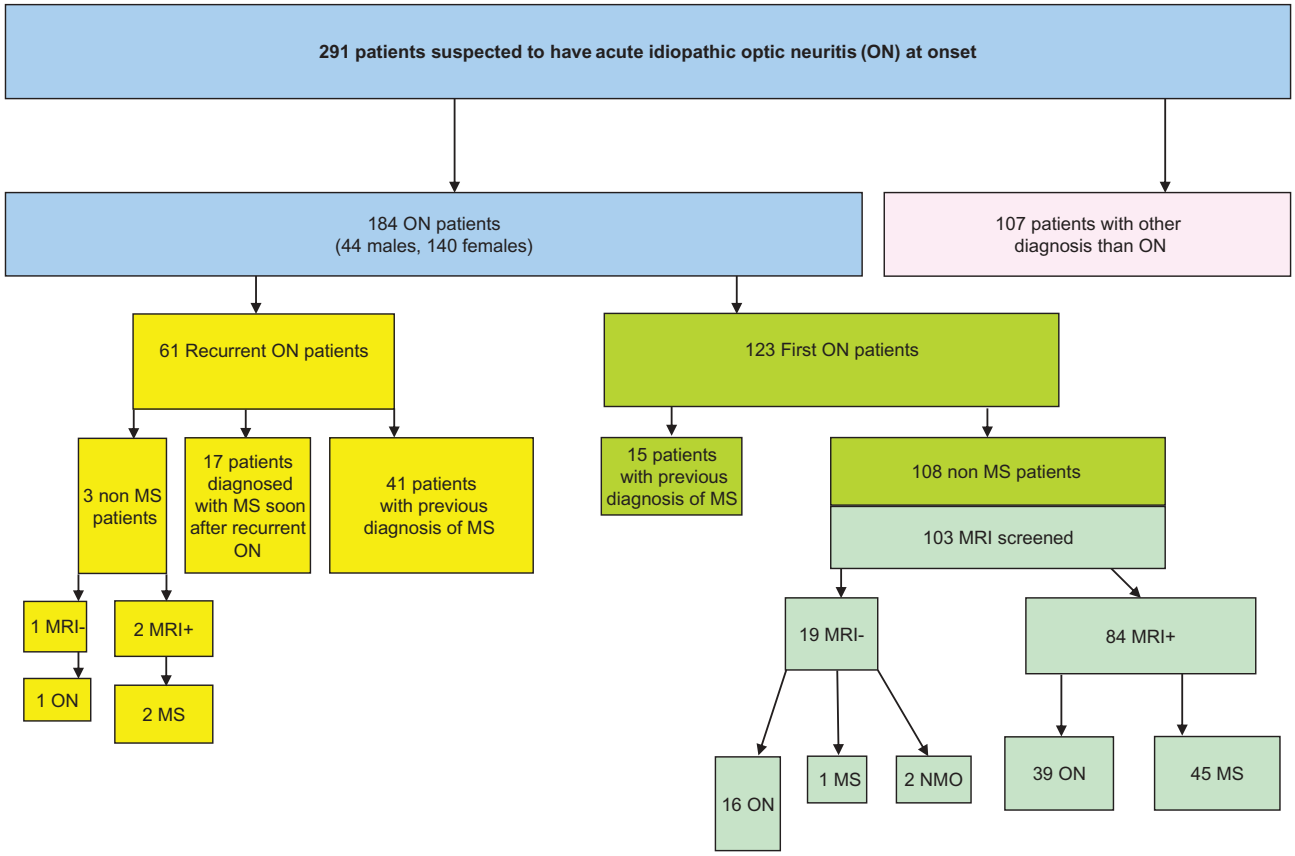


**Figure 2.** Flow chart of patient recruitment.

VEP), it is easier to make the differential diagnosis and, therefore, the incidence figures are becoming more reliable since some mimickers of ON can be differentiated from ON.[18–21] Our study found an incidence of 3.0 per 100,000, which is slightly higher than the earlier incidence 2.4 per 100,000 in Southern Finland from a period 1970 to 1978 when MRI and most of the other ancillary methods were not utilized[22]. It is likely that the incidence of ON has increased slightly more than the figures directly indicate, because of the probably lower number of false positive cases in our present study. On the other hand, the development of the health-care system in Finland may nowadays find more often the ON patients then during the previous study in the 1970s. Today, people also more actively search medical help with even minor symptoms, which may increase the incidence as well.

The incidence of ON varies a lot around the world (Table 2). The high incidence of 5.4 per 100,000 in a quite recent study from Spain[23] suggested that the incidence of ON is on the rise. The population of that study is quite small (300,000) and the study area is limited to a small part in Spain, Barcelona area, so these figures are not quite comparable to other studies. Northern Europe and Sardinia in Italy[29] are known to be areas with high

**Table 2.** Summary of epidemiological surveys on acute idiopathic optic neuritis (ON) in chronological order.

| | | | Annual incidence per 100,000 | | |
|---|---|---|---|---|---|
| Region | Study period | Population | Total | Male | Female |
| Finland (Uusimaa County) (present study) | 2008–2012 | 1.5 million | 3.0 | 1.4 | 4.6 |
| Spain (Barcelona area)[23] | 2008–2012 | 300,000 | 5.4 | 3.4 | 7.1 |
| Singapore[24] | 2002–2004 | 5.5 million | 0.8 | – | – |
| Croatia | 1985–2001 | – | 1.6 | 1.1 | 2.2 |
| - Split-Dalmatia County | 1977–2001 | | 2.2 | | |
| - Rijeka County[25,26] | | | | | |
| Sweden (Stockholm area)[27] | 1990–1995 | 1.6 million | 1.5 | 0.6 | 2.3 |
| USA (Olmsted County, Minnesota)[28] | 1985–1991 | – | 5.1 | 2.6 | 7.5 |
| Italy (Sardinia)[29] | 1977–1986 | – | 2.4 | – | – |
| Finland | 1970–1978 | 1.1 million | 2.4 | 1.5 | 3.2 |
| - Uusimaa County | | 430,000 | 2.3 | 1.8 | 2.8 |
| - Vaasa County[22] | | | | | |

incidence of MS. As ON is often related to MS, the lower incidence of ON in these areas compared to the Barcelona area is a bit surprising. The well-known observation that MS is quite rare in Asia is well correlated with the low incidence of ON in Singapore.[24]

Our study again confirmed that ON occurred more often in females (ratio, 3:1). Bilateral ON (1.6%) and NMO (1%) were rare. Almost a third (30%) of the patients had a previous diagnosis of MS. Moreover, of the patients who had ON as their first demyelinative episode, 82% had demyelinating MRI lesions (MRI+). The presence of any demyelinative lesions was a strong predictor of MS because 54% of MRI+ patients vs. 5% of MRI− patients developed MS during follow-up (positive and negative predictive value, 54% and 94%, respectively). Since MRI defines a subpopulation with a significant risk of MS, as has been shown previously,[30,31] an MRI scan should be considered in the routine diagnostic work-up of ON to facilitate early diagnosis and early treatment of MS. It is becoming increasingly clear that early treatment is more effective than delayed treatment in MS.[32] The practice of performing the MRI upfront, before any medical treatment, is also supported by our finding of six intracranial compressive lesions (2%) as mimickers of ON. In another recent study from the USA, 4% of suspected ON cases had optic sheath meningioma[33] illustrating that intracranial compressive lesions are not uncommon mimickers of ON. There are also reports of optic nerve lymphoma and optic nerve sheath melanoma cases as serious compressive lesions mimicking ON.[34,35]

About one third (36%) of the patients were eventually diagnosed with a disease other than ON and MRI especially aided in quick differentiation of ON from serious intracranial compressive lesions. Except the cases with intracranial expansion and one NAION patient who had optic disc swelling, MRI findings were unremarkable in patients who did not have ON. In our study, MRI was a very good predictor of ON diagnosis because only 5% of patients in the non-ON group had lesions in optic nerve or brain typical for ON patients as compared to 78% of patients in the group with first ON without previous diagnosis of MS. Nevertheless, it is of note that 18% of cases with their first ON did not have any lesions on MRI, stressing the importance of thorough clinical examination. The most common differential diagnosis was NAION, which often has similar acute symptoms and signs as ON. NAION patients, however, are typically older, male, have more often cardiovascular disease, and orbital MRI typically shows different results between patients clinically diagnosed with either ON or NAION.[36] The latter patients also typically have a small optic disk in both eyes ("disk-at-risk").

There are limitations of our study that affect the generalization of the results. First, the study population was focused on Southern Finland, and all patients were white Caucasians. Thus, these results do not directly apply to other ethnic groups with lower incidence of MS. Second, not all patients necessarily seek medical attention during an acute ON which may cause bias in case ascertainment; these include very mild cases and socially excluded citizens.

This study was approved by the Ethics Committee of the Hospital District of Helsinki and Uusimaa (Dnro 83/13/03/01/2013).

## Conflicts of interest

None of the authors have any proprietary interests or conflicts of interest related to this submission.

This submission has not been published anywhere previously and it is not simultaneously being considered for any other publication.

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