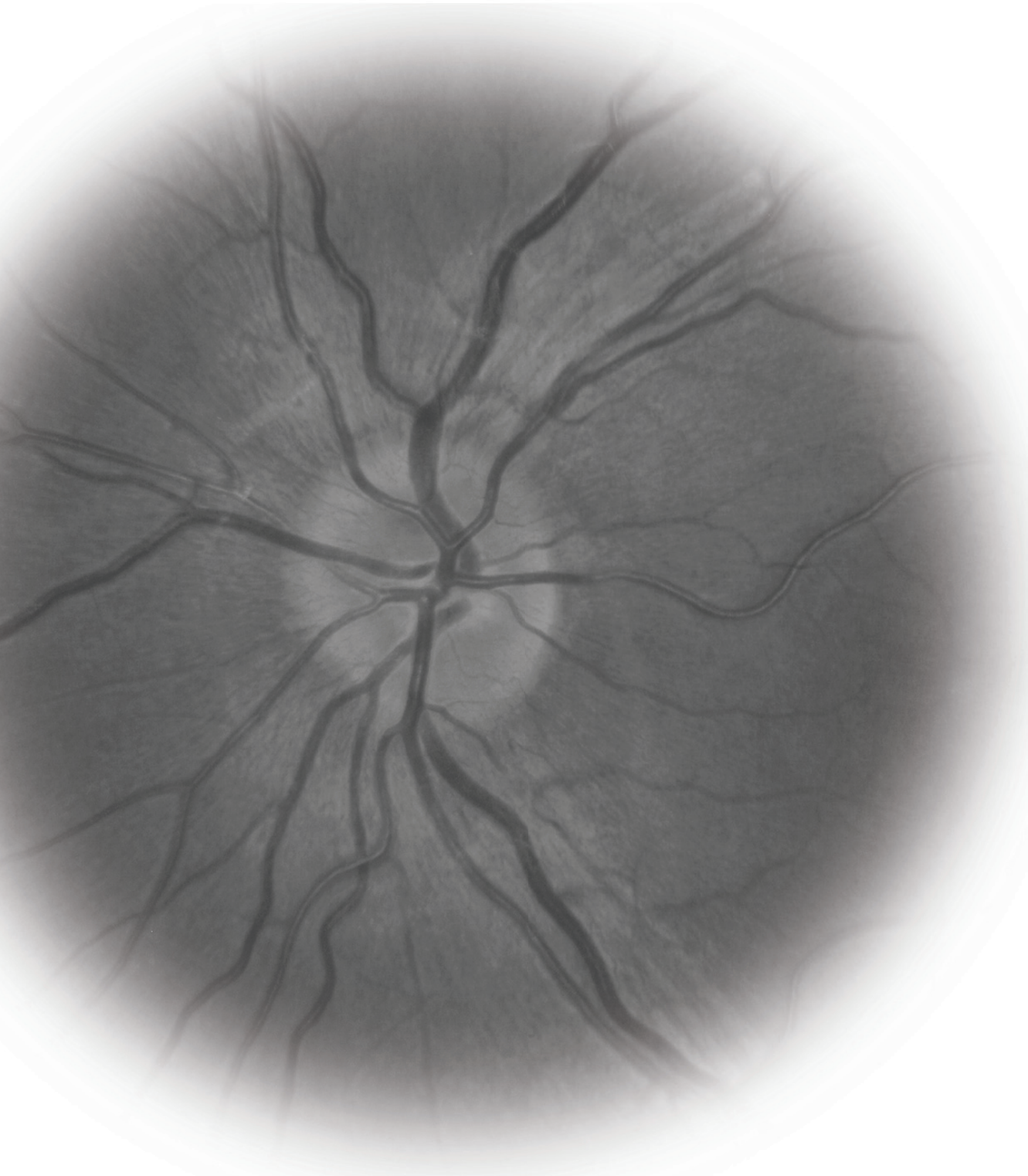**Mika Siuko**

# Optic Neuritis and Neuromyelitis Optica – Clinical and Genetic Aspects

Department of Ophthalmology, Faculty of Medicine,
University of Helsinki and Helsinki University Hospital,
Doctoral Programme in Clinical Research

# Optic Neuritis and Neuromyelitis Optica – Clinical and Genetic Aspects

**Mika Siuko**

ACADEMIC DISSERTATION

To be publicly discussed, with the permission of the Faculty of Medicine, University of Helsinki, In the Auditorium of The National Museum of Finland, Mannerheimintie 34, Helsinki, on September 27th 2019, at 12 noon

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*To Tiia and Elmeri*

# CONTENT

# LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications referred to in the text by their Roman numerals:

I       Siuko M, Kivelä TT, Setälä K, Tienari PJ. Incidence and Mimickers of Acute Idiopathic Optic Neuritis: Analysis of 291 Consecutive Patients from Southern Finland. Ophthalmic Epidemiology 2018;24:1-6.

II      Siuko M, Kivelä TT, Setälä K, Tienari PJ. The clinical spectrum and prognosis of idiopathic acute optic neuritis: A longitudinal study in Southern Finland. Multiple Sclerosis and Related Disorders, in press.

III     Siuko M, Tienari PJ, Saastamoinen KP, Atula S, Miettinen A, Kivelä T, Setälä K. Neuromyelitis optica and aquaporin-4 (AQP4) autoantibodies in consecutive optic neuritis patients in Southern Finland. Acta Ophthalmologica 2014;92(4):387-91.

IV      Siuko M, Valori M, Kivelä T, Setälä K, Morin A, Kwan T, Pastinen T, Tienari P. Exome and regulatory element sequencing of neuromyelitis optica patients. Journal of Neuroimmunology 2015;15;289:139-42.

# ABBREVATIONS

| | |
|---|---|
| A | Adenine |
| AION | Arteritic anterior ischaemic optic neuropathy |
| AMD | Age-related macular degeneration |
| AMPPE | Acute multifocal placoid pigment epitheliopathy |
| ANA | Antinuclear antibodies |
| AQP4 | Aquaporin-4 |
| AZOOR | Acute zonal occult outer retinopathy |
| BC | Breast cancer |
| BCVA | Best-corrected visual acuity |
| C | Cytosine |
| C3ORF20 | Chromosome 3 open reading frame 20 |
| C5ORF47 | Chromosome 5 open reading frame 47 |
| CADD | Combined annotation dependent depletion |
| CRP | C-reactive protein |
| CF | Counting fingers |
| CI | Confidence interval/Cerebral infarction |
| CIS | Clinically isolated syndrome |
| CNS | Central nervous system |
| CRVO | Central retinal vein occlusion |
| CSF | Cerebrospinal fluid |
| DNA | Deoxyribonucleic acid |
| DMT | Disease-modifying therapies |
| EBV | Epstein-Barr virus |
| ELISA | Enzyme-linked immunosorbent assay |
| ESR | Erythrocyte sedimentation rate |
| Fig | Figure |
| G | Guanine |
| GWAS | Genome-wide association studies |
| HLA | Human leukocyte antigen |
| HUSLAB | Clinical laboratory of the Helsinki University Hospital |
| ICD-10 | International Statistical Classification of Diseases and Related Health Problems, version 10 |
| IgG | Immunoglobulin G |
| IgG-i | Immunoglobulin G index |
| IL2RA | Interleukin-2 receptor alpha |
| IL7R | Interleukin-7 receptor |
| INO | Internuclear ophthalmoplegia |
| HLA | Human leukocyte antigen |
| Leuk | Leukocytes |

| | |
|---|---|
| LHON | Leber hereditary optic neuropathy |
| MEWDS | Multiple evanescent white dot syndrome |
| MfVEP | Multifocal visual evoked potential |
| MHC | Major histocompatibility complex |
| MOG-ab | Myelin oligodendrocyte glycoprotein antibodies |
| MOG-EM | Myelin oligodendrocyte glycoprotein associated encephalomyelitis |
| MRI | Magnetic resonance imaging |
| MRI- | Magnetic resonance imaging showed no demyelinating lesions |
| MRI+ | Magnetic resonance imaging showed demyelinating lesions |
| MS | Multiple sclerosis |
| msec | Millisecond |
| NAION | Non-arterial ischemic optic neuropathy |
| NMO | Neuromyelitis optica |
| NMOSD | Neuromyelitis optica spectrum disorders |
| OCB | Oligoclonal bands |
| OCT | Ocular coherence tomography |
| ON | Optic neuritis |
| ONTT | Optic neuritis treatment trial |
| P | Protective allele |
| PLB1 | Phospholipase B1 |
| Prot | Protein |
| Pt | Patient |
| PZDA2 | PDZ domain-containing protein 2 |
| Q1 | January-March |
| Q2 | April-June |
| Q3 | July-September |
| Q4 | October-December |
| R | Risk allele |
| RAPD | Relative afferent pupillary defect |
| RNFL | Retinal nerve fibre layer |
| RRMS | Relapsing-remitting multiple sclerosis |
| SNP | Single-nucleotide polymorphisms |
| T | Thymine |
| TM | Transverse myelitis |
| VA | Visual acuity |
| VEP | Visual evoked potential |
| ZNF606 | Zinc Finger Protein 606 |

# ABSTRACT

Optic neuritis (ON) is caused by immune-mediated demyelination of the optic nerve. In ON the visual acuity of the patient usually decreases in one eye. Common additional symptoms include impaired colour vision, pain with eye movements, and pupillary dysfunction. While ON may present as a single episode, in about 20% of patients it is the first symptom of multiple sclerosis (MS). Approximately half of patients with MS are affected by ON at some stage of the disease. MS typically causes demyelination in the optic tract, cerebrum, brainstem, and spinal cord; MS symptoms are therefore extensive. With the revised diagnostic criteria of MS, the diagnosis of MS may sometimes be confirmed already after the first episode of ON. In addition to MS, another demyelinating disease associated with ON is neuromyelitis optica (NMO), also known as Devic disease. As the diagnostic criteria for this disease have recently evolved the most common term is neuromyelitis optica spectrum disorders (NMOSD). NMOSD is characterized by demyelinating changes in the spinal cord and an increased aquaporin-4 (AQP4) antibody index. There are currently no treatments that improve the prognosis of ON. However, high-dose corticosteroids may reduce the duration of symptoms and some medications may reduce the risk of MS development among patients with ON. The diagnosis of ON is demanding as the diagnosis is based on exclusion of other causes. Little is known about the factors that affect the natural course of ON. Severe visual impairment may result after multiple recurrences.

We analysed the natural course of ON and its differential diagnosis, clinical findings, incidence, and connection to MS in Southern Finland during the period from 2008 to 2012. In addition, we studied the prevalence of NMO associated with ON in southern Finland and the development of NMO diagnostics. We also analysed genetic mutations by exome sequencing in NMO patients in Southern Finland.

We observed that the incidence of ON in Finland has increased. This may be due to improved diagnostic methods and because diagnostic delay is briefer as patients nowadays actively seek medical attention with even minor symptoms. The seasonal variation in the number of ON diagnoses was also confirmed.

The challenges in diagnosing ON wereas notable, as over one third of patients with suspected ON at onset were later diagnosed with a disease other than ON.

Our study confirmed that ON occurs more frequently in women (F:M ratio 3:1) and most cases is related to MS. Both bilateral ON (1.6%) and NMO (1%) are rare in Finland. The natural course of ON showed good recovery; approximately 70% of patients achieved visual acuity >0.8 (average follow-up time of 38 days). When analysing the factors that affect prognosis for patient visual impairment, our data suggest that in addition to baseline visual acuity, optic disc swelling and lesions in the optic nerve on magnetic resonance imaging (MRI) are associated with poorer prognosis.

Nearly one-third (30%) of patients were already diagnosed with MS before diagnosis of ON. Among patients with their first ON, 82% were diagnosed with demyelinating changes in brain MRI.

Demyelinating changes in brain MRI were a significant risk factor for MS; 54% of ON patients with early-stage demyelination in brain MRI developed MS (average follow-up time of 7 years). Only 5% of those without demyelinating changes in brain MRI developed MS. The practice of performing MRI before any medical treatment was also supported by our finding of six intracranial compressive lesions (2%) as mimickers of ON.

We investigated the sensitivity and specificity of the AQP4 antibody assay in the diagnosis of NMO in our ON patient cohort. The number of patients with NMO was very low (n=2). The AQP4 antibody test sensitivity was only 1/2 and had a positive predictive value of 1/3.

The exome sequencing study of patients with NMO (n=5) was the first published study of this kind in this disease. No genetic variants common to all patients were found. Four of the mutations were shared by two patients with NMO (C3ORF20, PDZD2, C5ORF47, and ZNF606). Another PDZD2 variant was also found in a third patient. Additionally, two rare, probably functional variants in the non-coding region of DNA were found in two patients. The significance of these findings cannot yet be evaluated. However, as extensive research in this field is ongoing we assume that the role of these variants will be revealed in the future.

# INTRODUCTION

Typical optic neuritis (ON) is regarded as the most common type of ON. It is related to multiple sclerosis (MS) in most cases. Atypical ON is a large concept, including several aetiological causes, where neuromyelitis optica spectrum disorders (NMOSD) are regarded as the most prevalent cause. Separation of these entities is essential for prognosis and treatment.

ON is an inflammation of the optic nerve, which is also known as cranial nerve II. ON causes visual impairment via multiple mechanisms. The most common symptoms are decreased visual acuity, pain during eye movements, visual field defects, impaired pupillary light reflex, and loss of colour vision.

Most patients are young adults with peak manifestation between the ages of 20 and 40. Women are more frequently affected (Beck et al. 1992, Jin et al. 1998, Wakakura et al. 1999, Zhang et al. 2007, Lim et al. 2008, Soelberg et al 2017).

The incidence of ON varies around the world and is highest in populations located at higher latitudes such as Nordic countries and the USA, where the incidence of MS is high as well (Sumelahti et al. 2000, Langer-Gould et al. 2013, Sumelahti et al. 2014).

Typical ON is closely related to MS and is the presenting symptom in about 20% of MS cases. ON occurs at some point of the disease in about half of MS patients (Foroozan et al. 2002, Arnold et al. 2005, Frohman et al. 2005). Diagnostic procedures follow the diagnostic criteria in MS.

NMOSD, also called neuromyelitis optica or Devic disease, is characterized by ON and longitudinally extensive myelitis and often leads to severely impaired mobility and reduced visual acuity. With the evolving diagnostic criteria from 2015, area postrema syndrome (vomiting and hiccups), recurrent ON without myelitis, and recurrent myelitis without ON are also included in diagnostic criteria (Weinshenker et al. 2006, Wingeschuk et al. 2015). The most widely used medications for NMOSD are the immunosuppressive drugs azathioprine, rituximab, mycophenolate mofetil, and intravenous immunoglobulins. The efficacy of these drugs in the treatment of NMOSD is low (Huh et al. 2014, Viswanathan et al. 2015, Damato et al. 2016, Bichuetti et al. 2018).

Aquaporin-4 (AQP4) autoantibodies are considered an important adjunct for diagnosing NMOSD. AQP4 autoantibodies target the water channel AQP4 located in the foot processes of astrocytes (Jarius et al. 2007, Misu et al. 2007, Popescu et al. 2015). This autoantibody has shown high sensitivity and specificity in the diagnostics of NMOSD (Lennon et al. 2004).

While there are no proven effective therapies for ON, some medications (such as interferons) may reduce the risk of MS development among patients with typical ON (Comi et al. 2001, Galetta et al. 2001, Comi et al. 2009, Kappos et al. 2016). After a definite diagnosis of ON, treatment with high-dose intravenous corticosteroid is the most common treatment around the world but has only modest efficacy. Although high-dose intravenous corticosteroids may reduce the period of acute visual dysfunction, results from a large trial that included 457 patients revealed that the visual outcome after 6 months is similar regardless of corticosteroid treatment (Beck et al. 1992). Most patients have good recovery in a few weeks after onset but in some cases of ON visual acuity may be permanently reduced.

# REVIEW OF THE LITERATURE

## 1.　　Clinical aspects of optic neuritis

### *1.1　　Definition and diagnosis of ON*

In ICD-10, ON (H 46) is defined as an inflammation targeting the optic nerve and impairing its function. A typical diagnosis of ON is considered when the disease is related to demyelinating diseases.

Anatomically, ganglion cell axons form the optic nerve and oligodendrocytes produce the myelin around it. The optic nerve transmits signals from the retina to the visual cortex of the brain first via the optic chiasma, where they partly cross over (decussate) to the opposite side of the brain and continue to the optic tract, lateral geniculate nucleus of thalamus, and optic radiations (Figure 1).
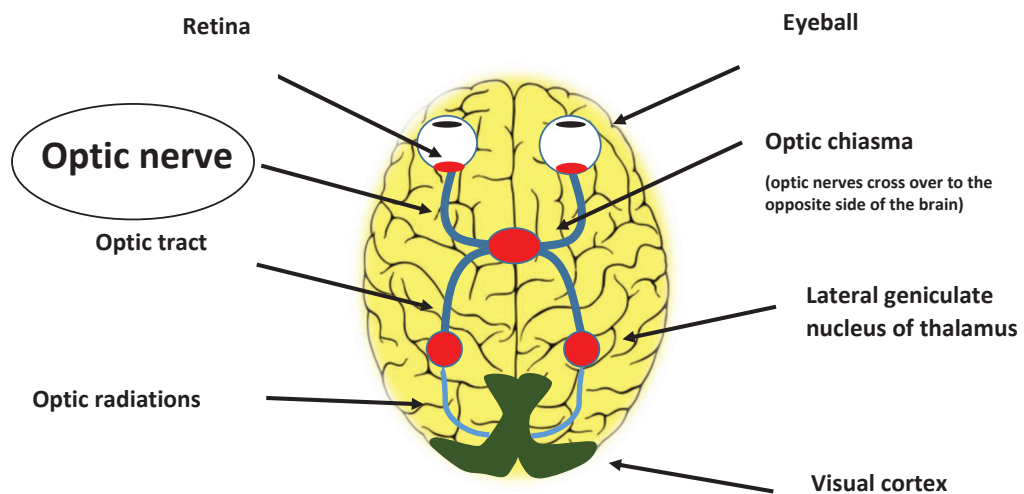


**Figure 1.** The visual pathway. Copyright: Mika Siuko

### *1.2　　Diagnostic criteria*

The diagnosis of typical and atypical ON is clinical and no universal diagnostic criteria are available. The most common criteria are a combination of acute or subacute loss of vision associated with relative afferent pupillary defect (RAPD), pain upon eye movements, and some degree of acquired colour vision deficiency. Visual field defects, changes in visual evoked potentials (VEP), and MRI findings support the diagnosis of ON (Beck et al 1992).

## *1.3    Symptoms*

Much of our current knowledge of the clinical features of ON comes from the Optic Neuritis Treatment Trial (ONTT) (Beck et al. 1992), conducted more than 25 years ago and cited about 800 times to date. The ONTT enrolled 457 patients who had acute unilateral ON. The two most common symptoms recorded in this trial were vision loss in one eye and ocular pain.

Visual loss usually develops during a short period. Loss of vision can be minor, but sometimes the visual acuity of the patient is very low with almost no light perception. While most ON episodes are unilateral, bilateral cases can be found as well, especially among children.

Ocular pain in ON typically worsens with eye movements. This was the second most common symptom recorded in the ONTT. Patients with ON sometimes also see flickering or flashing lights with eye movements.

Loss of colour vision is a common symptom of ON. Patients may notice that colours appear less vivid than normal (Figure 2). Loss of visual field is a typical symptom of ON as well, but patients often do not notice this change themselves.



Simulation of ON                    Normal vision

**Figure 2.** Patient suffering from ON often describes sight as fuzzy or blurry (Picture from Hietalahti harbour, Helsinki, Finland).

## 2.    Incidence of ON

### *2.1    History of ON*

The first clinical description of visual signs related to demyelinating diseases is considered to be that of Augustus d'Esté (1794-1848), the great-grandson of George III and the nephew of Queen Victoria, who had the disease in the early 19th century. One very probable case was a young Dutch woman, Lidwina van Schiedam, whose illness started in 1296, at the age of 16, and lasted 37 years. She eventually was paralysed in both legs and in the right arm with facial palsy, bilateral loss of vision, sensory changes, and dysphagia. There is also a Viking saga about a woman whose symptoms might have been caused by MS or acute encephalomyelitis: "A woman called Halla got such a bad illness on Saturday *infra octaves Beatae Virginis* that she lost the sight of both eyes, and on the next day she lost her speech, then she made a vow in her mind, with the advice of those who stood by, to almighty God for cure and to the holy bishop Thorlakr for intercession, to walk to Skaholt and fast on bread and water before Thorlaks mass, and some prayers in addition. On the third day a candle-wick was put around her head, and she then recovered the sight of one eye, and was able to open both. On Sunday she recovered her speech and on the feast of St. Michael during the elevation of the host she recovered the sight of the eye that had previously been blind" (Poser et al 1994). The earliest references related to dysfunction of the optic nerve with vision loss are found in Arabic texts from the 9th century. The clinical profile of ON had been well established by the end of 19th century. The ophthalmoscope was invented in 1851, which allowed ophthalmologists sometimes to localize the visual loss to the optic nerve.

The relationship of ON with MS has been noted for as long as ON has been recognized. Dr. Thomas Buzzard reported in 1893 five patients with a history of MS that had episodes of visual failure with recovery consistent with ON. In the beginning of the 20th century, some controversy still existed on the relationship of ON to MS. In 1930, Dr. James Adie asserted that MS accounted for all cases of ON.

Sir Thomas Clifford Albutt (1836-1925) described in 1870 the syndrome now known as NMOSD. He observed that some patients with co-existent transverse myelitis and ON had a severe disease course. In 1894, Eugène Devic (1858-1930) and his graduate student, Fernand Gault, found 16 patients with severe unilateral or bilateral vision loss, who within a short period developed spastic weakness of the limbs, loss of sensation, and incontinence. At that time, this disease was described as a monophasic disorder of bilateral ON and TM. Currently NMOSD is recognized as a relapsing disorder with many manifestations (Wingerchuk et al. 2015).

## 2.2 Incidence studies globally

Epidemiological studies in demyelinating diseases date from the early 1900s for MS and as recently as the late 1990s for NMODS. Today the highest occurrences of MS are found in the Nordic countries, the British Isles, and the countries settled by their immigrants, namely, the USA, Canada, Australia, and New Zealand. These observations have prompted a hypothesis that the genetic background of the Vikings might lie behind the genetic susceptibility to ON in those areas and in other parts of the world (Poser 1995). Since ON is often linked with MS, the prevalence of ON also is high in these areas. In Finland the highest incidence of MS and ON is found in Western Finland, especially in the Southern Ostrobothnian region. The distinctive settlement history of that area and molecular genetic evidence suggest that a genetic founder effect plays an important role in the high MS risk in that area (Tienari et al. 2004).

There are only a few studies on the incidence of ON from around the world and the diagnostic methods are variable (Table 1). The incidence varies greatly from a very high incidence of ON in the Barcelona area in Spain (5.36 per $10^5$) to very low in Singapore (0.83 per $10^5$).

The incidence figures today are more reliable as modern diagnostic modalities (e.g. MRI, VEP, OCT) facilitate the differential diagnosis (Chan 2012, Berg et al. 2015).

**Table 1.** Results of ON incidence studies around the world.

| Country | Study period | Population | Crude incidence per $10^5$ | | |
|---|---|---|---|---|---|
| | | | Total | Male | Female |
| Denmark (Soelberg et al. 2017) | 2014-2016 | 994,000 | 3.28 | 2.02 | 4.57 |
| Spain (Barcelona area) (Martínez-Lapiscina et al. 2014) | 2008-2012 | 300,000 | 5.36 | 3.36 | 7.13 |
| Singapore (Lim et al. 2009) | 2002-2004 | 5.5 million | 0.83 | - | - |
| Croatia  - Split-Dalmatia County  - Rijeka County (Bojic et al. 2004 and Loncarek et al. 2005) | 1985-2001 1977-2001 | - - | 1.6 2.18 | 1.1 | 2.2 |
| Sweden (Stockholm area) (Jin et al. 1995) | 1990-1995 | 1.6 million | 1.46 | 0.59 | 2.28 |
| USA (Olmsted County, Minnesota) (Rodriquez et al. 1995) | 1985-1991 | - | 5.1 | 2.6 | 7.5 |
| Italy (Sardinia) (Congia et al. 1989) | 1977-1986 | - | 2.4 | - | - |

# 3. Clinical and paraclinical findings

## 3.1 *Visual acuity loss*

Visual acuity loss is the most common symptom of ON and can easily be verified by a vision test chart (Figure 3). Because of the common visual field defects related to ON, the visual acuity of the patients may vary considerably depending on whether they are looking straight forward or whether they are tilting their head. At the onset of ON visual loss may be quite minor, but visual acuity often decreases during the first 2 weeks of an acute episode of ON.
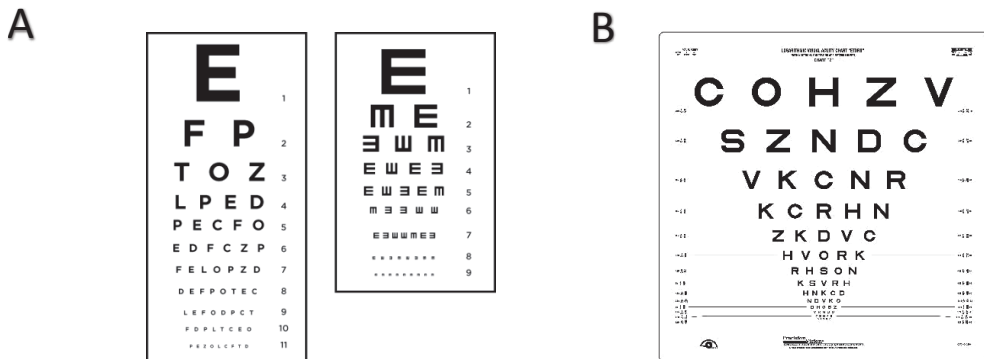


**Figure 3.** Visual acuity is often measured by a Snellen chart (A). The Early Treatment Diabetic Retinopathy Study (ETDRS) chart, also known as a LogMAR chart (B), is often used in research settings to measure visual acuity. Measurements by the ETDRS chart are considered more precise but also more time consuming.

## 3.2 *Pupillary light reflex*

A RAPD is often observed in the affected eye in patients with ON because the other eye usually is unaffected and healthy. To test the RAPD, a swinging light test in a dark room with the patient fixating on a distant target is performed (Figure 4). When light is shone in one eye of a normal subject, both pupils will constrict equally. The pupillary reaction in the illuminated eye is the direct response, and the reaction in the fellow eye is the consensual response. The afferent pupillary fibres hemidecussate in the chiasm, as do the pupillomotor fibres in the brainstem. This double hemidecussation enables equal pupillary innervation and equal pupil size. There is also some evidence that the constriction velocity and constriction ratio of the pupil may help in differential diagnosis of acute and chronic ON and in non-arteritic idiopathic optic neuropathy. Pupillary constriction velocity, constriction ratio, and latency are significantly decreased in the acute phase of ON and non-arterial ischemic optic neuropathy (NAION) compared to normal controls. ON showed delayed constriction latency compared to NAION. Decreased pupillary light reflex is observed in the chronic phase of ON but not in NAION (Yoo et al. 2017).

**Right eye**     **Left eye**

**Pupils in the dark**

**Light to the healthy right eye – pupils constrict**

**Light to the affected left eye – both pupils dilate**

**Light to the healthy right eye – pupils constrict**
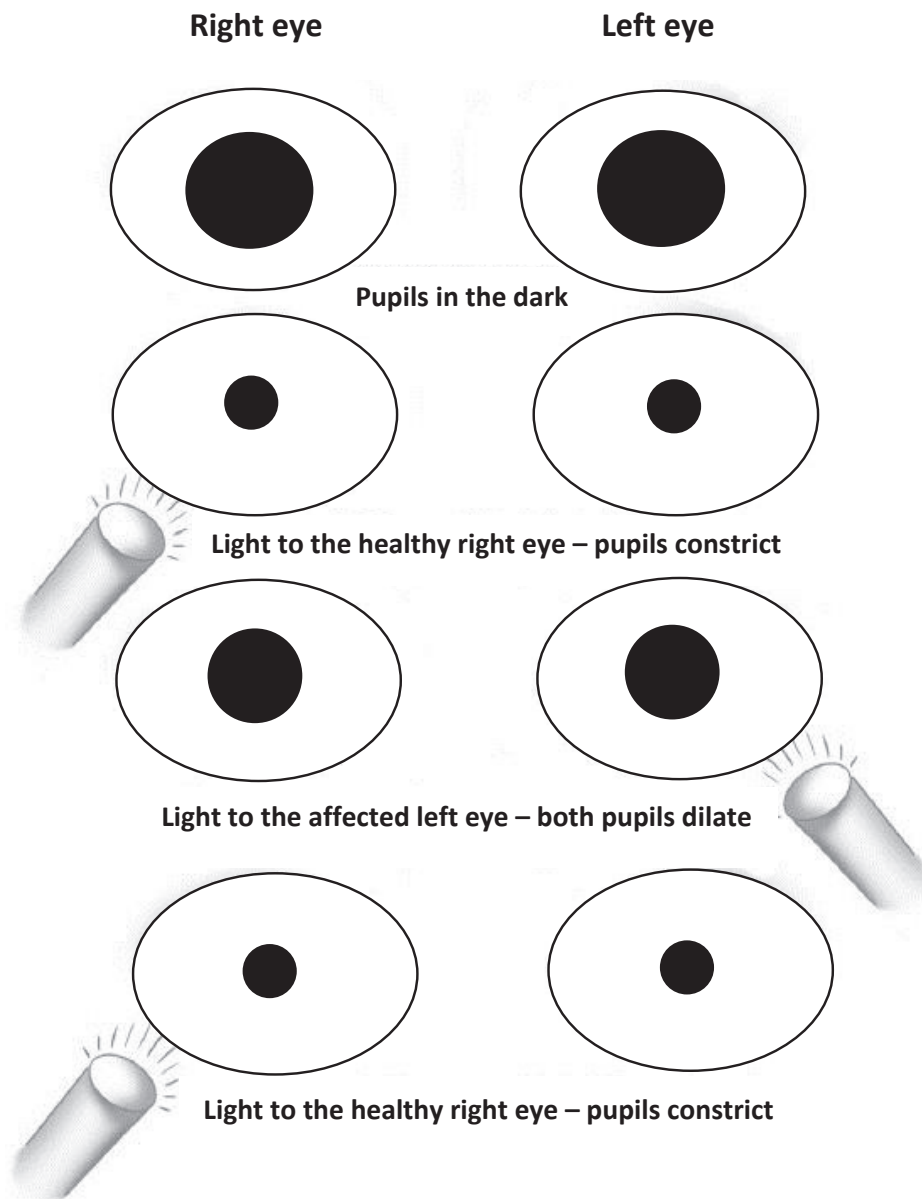
**Figure 4.** The swinging flash light test for relative afferent pupillary defect (RAPD) in a patient with ON in the left eye. If the pupil does not constrict or dilates when illuminated an ipsilateral RAPD is present, which suggests impaired function of the optic nerve, a typical finding in ON.

### 3.3     *Funduscopy*

Funduscopy is normal in most cases of ON in adults (Beck et al. 1992). However, it is common that some swelling of the optic nerve head of the affected eye is observed (papillitis), especially among children (Morales et al. 2000, Yeh et al. 2016) (Figure 5). If

there is no swelling of the optic nerve head, the condition is called retrobulbar neuritis. In these cases, the inflammation is located behind the eye. Since a patient with retrobulbar ON often has no clinical findings in the funduscopic examination the condition is often described as "neither the patient nor the doctor can see anything."

**A**                                    **B**



**Figure 5.** A normal optic disc (A) and a swollen optic disc (B) of a 23-year old woman with ON in left eye (Images from Helsinki University Hospital imagenet database).

### 3.4      *Colour vision*

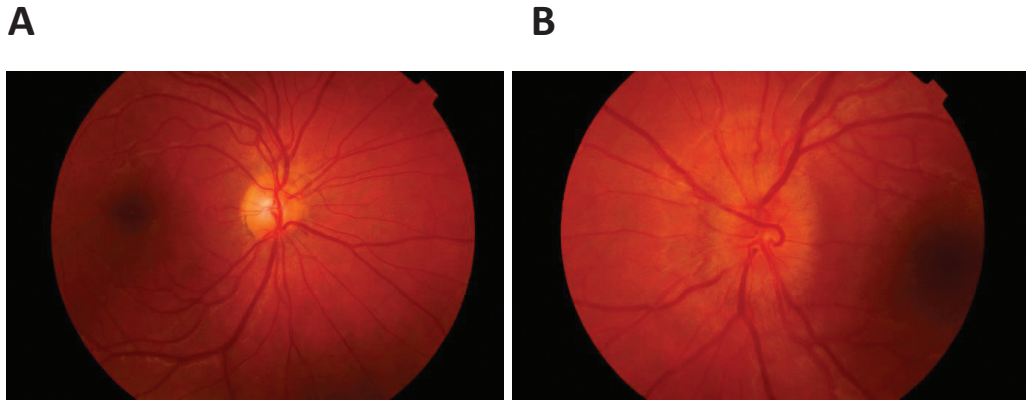Abnormal colour vision can be determined qualitatively by the Ishihara test (Ishihara Instructions of The Series of Plates Designed as a Test for Color Deficiency Shinobu Ishihara M.D., Dr. Med. Sc. Professor Emeritus of the University of Tokyo) (Figure 5) or quantitatively by the Farnsworth-Munsell 100 hue test (Farnsworth 1943) (Figure 6). The most common patterns of colour vision loss in ON at the time of the acute episode is blue/yellow defects (tritanomaly) and reduced sensitivity of red (protanomaly) and green (deutranomaly) after a 6-month follow up. Red/green defects are also present most of the time already in the acute phase of ON. In clinical practice, a red/green defect is the most common finding since very few people test the blue/yellow defects. An Ishihara test only finds red-green defects and is therefore not as useful as the Farnsworth-Munsell 100 hue test in determining the colour vision changes of an ON patient. The likelihood of persistent dyschromatopsia after 6 months is related to the severity of initial visual acuity loss (Katz 1995, Felgueiras et al. 2016).

The Ishihara test consists of several colored plates, each of which contains a circle of dots appearing randomized in colour and size (Figure 5). There are dots that form a number or a shape visible to people with normal color vision but are invisible or very difficult to see for those with a red-green colour vision defect. Other plates are designed to show numbers only to those with a red/green colour vision deficiency and invisible to those with normal red/green color vision. The full test consists of 38 plates. A severe deficiency is usually

apparent already after a few plates. There is also an Ishihara test consisting of a smaller number of plates (10, 14, or 24 plates).
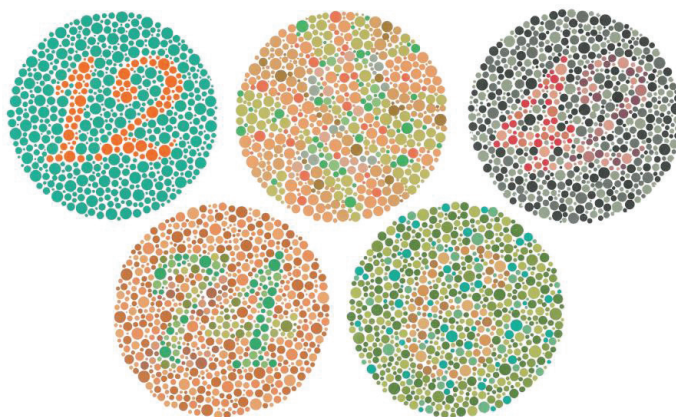


**Figure 6.** The Ishihara colour vision test for red-green colour deficiencies was published in 1917 and is named after its designer, the Japanese ophthalmologist prof. Dr. Shinobu Ishihara at the Imperial University of Tokyo.

A common color arrangement test is the Farnsworth-Munsell 100 Hue Color Vision Test (Farnsworth 1943). This test is used to provide a detailed analysis of colour blindness, the ability to accurately perceive colours, or both. The Farnsworth-Munsell 100 Hue Color Vision Test consists of 85 coloured plates, which have to be arranged in the correct colour order (Figure 6).



**Figure 7.** Farnsworth-Munsell 100 hue color vision test was invented in 1943 by Dr. Dean Farnsworth in the USA. In this test, the patient is expected to arrange the colour plates in correct order.

### 3.5    Visual fields

A visual field test of an acute ON patient by computerized perimetry often reveals a diffuse or central defect (Figure 8). During subsequent follow ups these visual field defects often disappear or became arcuate or paracentral defects. The high prevalence of visual field defects among patients with ON was revealed in the ONTT. At baseline, 100.0% of the visual fields from the affected eyes and 74.7% of the visual fields from the uneffected eyes were abnormal. After a 1-year follow up, approximately 50.0% of the affected eyes still had an abnormal visual field.

At baseline, 66.2% of the abnormalities in the affected eyes consisted of diffuse loss, which included total loss, central, centrocaecal, and widespread loss; 33.6% of abnormalities were localized loss. In contrast, the abnormalities found in the uneffected eyes rarely included total or central loss (Keltner et al. 2010).
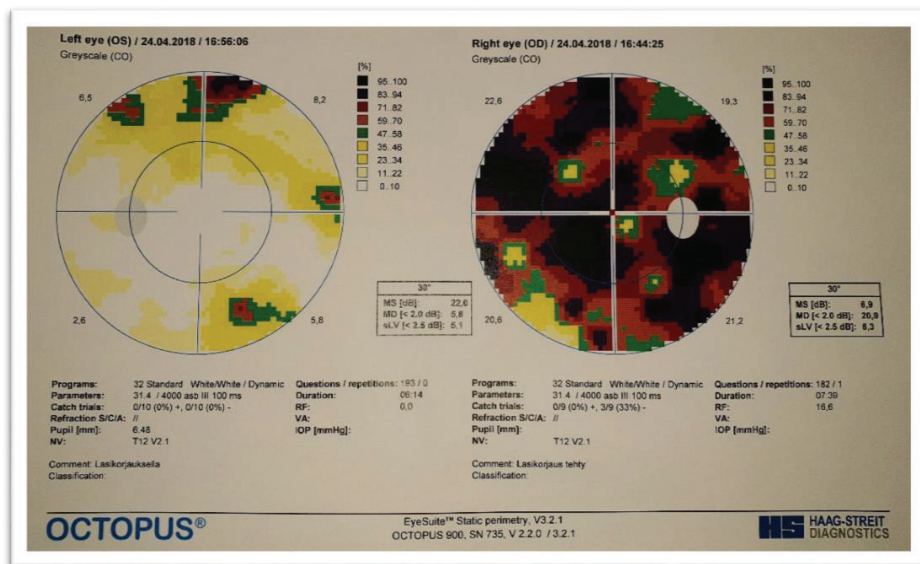


**Figure 8.** Octopus visual fields test of a 26-year old woman with ON in the right eye. A close to normal visual field in the left eye (left side of the picture) and severe diffuse visual field defects in the right eye (right side of the picture) were observed.

### 3.6    Visual evoked potential

The VEP measures the time for a visual stimulus to travel from the eye to the occipital cortex in the brain. Any abnormality that affects the visual pathways or visual cortex of the brain can alter the VEP. ON patients therefore often have changes in the signal amplitude and latency in VEP tests (Figure 9). These changes can often be found even after the visual acuity of the affected eye has recovered (Halliday et al 1972, You et al. 2011). A new

technique to measure VEPs is the multifocal VEP (mfVEP) that is designed to detect small abnormalities in optic nerve transmission and to provide topographic correlation along the visual pathway. Some studies have confirmed that visual field abnormalities correlate with the abnormalities detected by mfVEP (Pihl-Jensen et al. 2017).
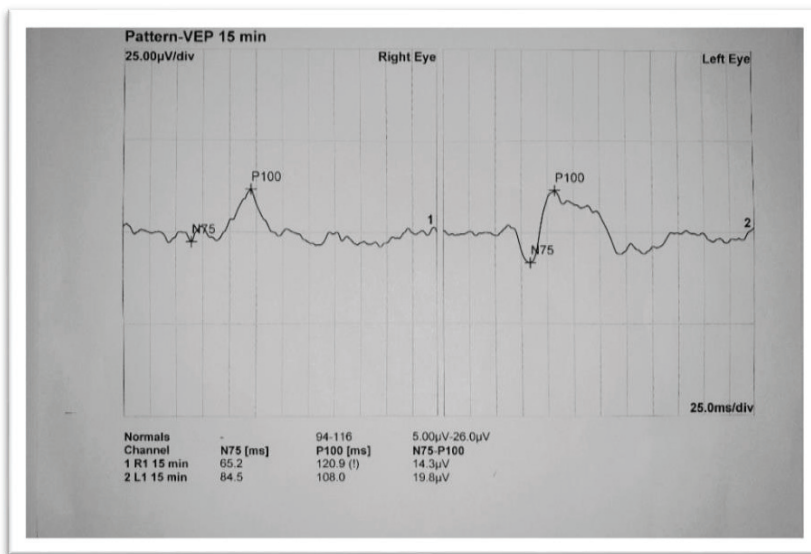


**Figure 9.** VEP measurements of a 26-year old woman with ON in the right eye (same patient as in Figure 8). ON decreases the amplitude and increases the latency of the VEP signal where the P100 component (100 ms after light stimulus) is delayed, which often occurs in association with optic nerve disease (left side of the picture).

### 3.7    OCT

Optical coherence tomography (OCT) is a non-invasive imaging technique to visualize and measure the thickness of the retina layers and the optic nerve head and therefore is useful in diagnosis and follow up of patients with ON (Figure 10). OCT confirms the presence of optic disc oedema in optic nerve head and quantifies the degree of axonal loss that follows the episode. OCT can detect subclinical changes in eyes with normal visual fields and normal visual acuity. RNFL thickness correlates with visual and neurological functioning and with disease duration. In addition to thinning of the RNFL, OCT studies have shown ganglion cell loss among ON patients (Britze et al. 2017, Soelberg et al 2018). Many studies have also documented that RNFL loss also occurs in the asymptomatic eye of an ON patient. Previous studies have revealed RNFL thinning in patients with MS who have not yet had an ON episode (Oberwahrenbrock et al. 2012, Huang-Link et al. 2015). OCT is also considered sensitive and specific in the differential diagnosis of optic nerve head drusen and optic disc oedema (Lee et al. 2011, Flores-Rodriquez et al. 2012, Rebolleda et al. 2017). In addition to ON diagnosis, OCT is used mostly to diagnose age-related macular

degeneration (AMD) (Hee et al. 1996, Adhi et al. 2013). OCT use in the diagnosis and follow up of glaucoma is also increasing (Hoh et al. 2000, Jia et al. 2014).
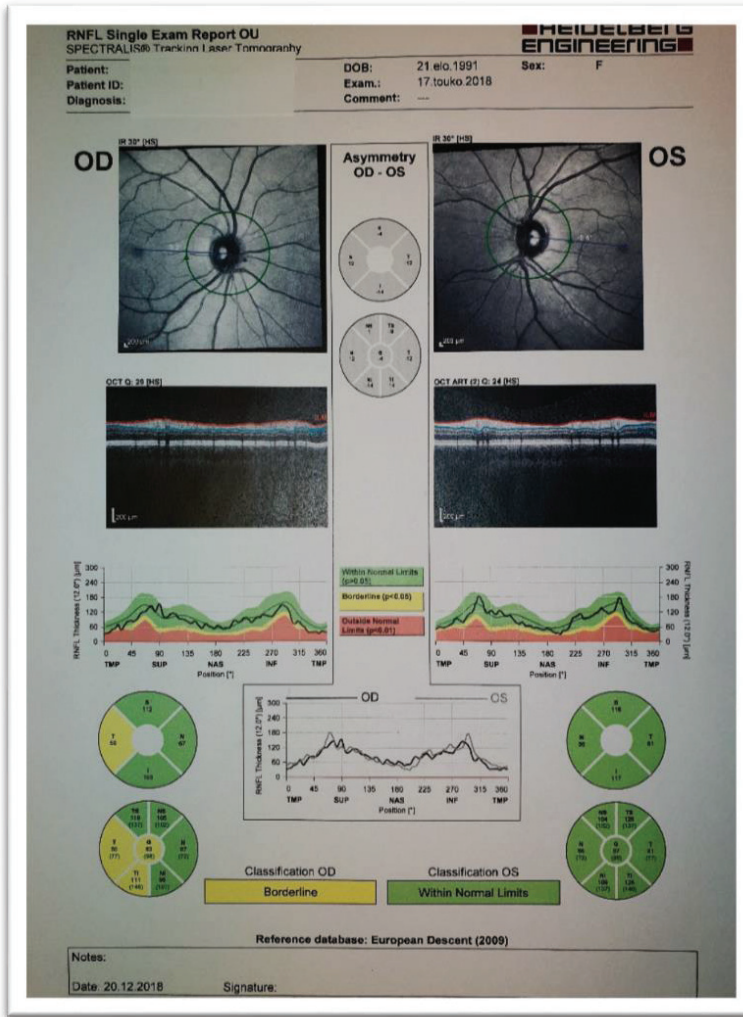


**Figure 10.** OCT of optic nerves of a 27-year old woman. At the time of OCT she had symptoms related to her first ON for 5 days. RNFL analysis demonstrates some borderline (yellow color) abnormalities in the temporal quadrant of the right eye. All quadrants of the left eye were normal (green color).

### 3.8    Laboratory tests

Laboratory tests are performed to facilitate exclusion of other diseases that mimic ON. In addition to a complete blood count, common laboratory tests to discover possible inflammatory processes are C-reactive protein (CRP) and erythrocyte sedimentation rate

(ESR). For the differential diagnosis of sarcoidosis and vasculitis, antinuclear antibodies, angiotensin-converting enzyme, and anti-neutrophil cytoplasmic antibodies are measured. To exclude an infectious origin of ON, for example neuroretinitis, antibodies for syphilis, cat-scratch fever, and *Borrelia burgdorferi* should be measured as well. Leber hereditary optic neuropathy (LHON) may also mimic ON and can be diagnosed with genetic testing of mitochondrial DNA. When NMOSD (see chapter 4.4) is suspected, the level of AQP4 is measured as well. Cerebrospinal fluid analysis is seldom used in the evaluation of patients presenting with a typical acute ON, but may yield important additional information in the diagnostics of atypical cases. Typically, the only CSF abnormality in patients with ON are oligoclonal bands (OCB), which are associated with an increased risk of developing MS (Rolak et al. 1996).

### 3.9    MRI imaging

MRI of the brain and the orbits is a common procedure to diagnose ON and exclude other diseases that might cause symptoms that mimick ON (Miller at al. 1988) (Figure 11). ON is often identified as a unilateral optic nerve swelling with a hyperintense MRI T2-sequence with contrast enhancement. Brain MRI may also show demyelinating changes that often are related to ON (Lee et al. 2009). In the future, multiple novel approaches, like orbit-specific MRI coils, quantitative sequences, and rapid acquisition techniques, may improve our ability to study optic nerve pathologies and characterize the optic nerves (Hoch et al. 2017). When NMOSD is suspected, MRI of the spinal cord is performed. The demyelinating lesions of a patient with NMO typically extend over three or more segments of the spinal cord and may reach the medulla oblongata and brainstem (Figure 12).
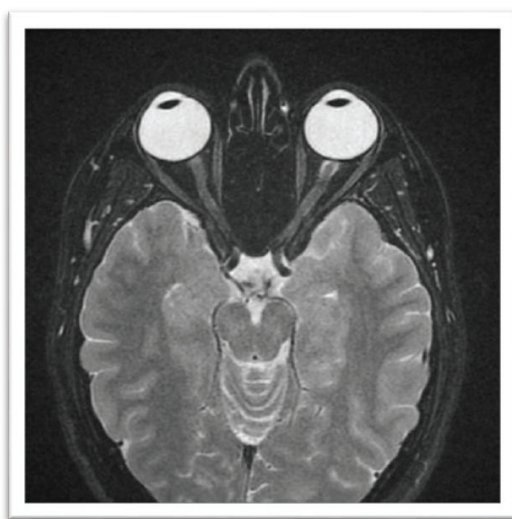


**Figure 11.** MRI T2-sequence of the brain and the orbits of an MS patient with left-sided ON. The retrobulbar segment of the optic nerve on the left side appears swollen and gives a hyperintensive signal (Image from Helsinki University Hospital MRI-image database).

**A**

**B**
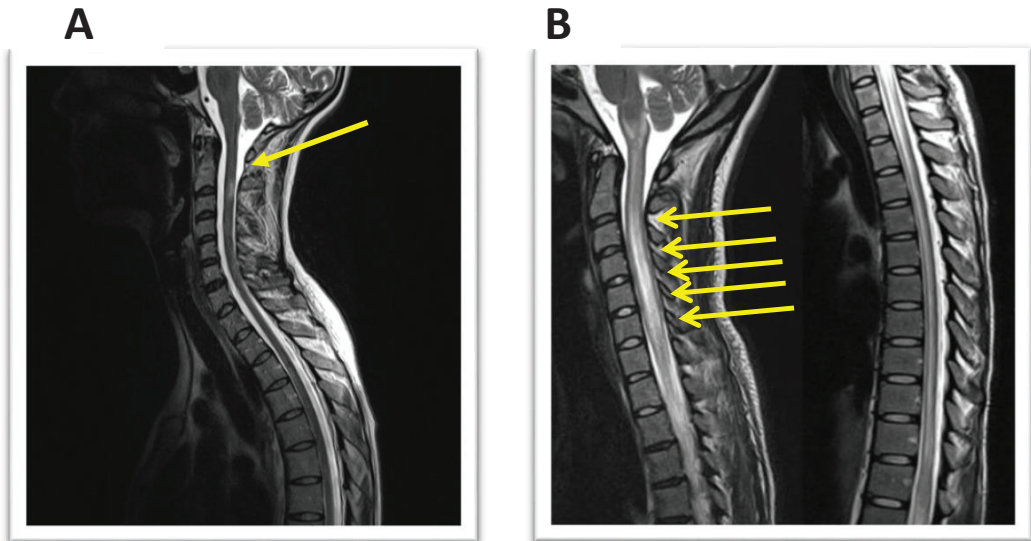


**Figure 12. A.** Spinal cord MRI of an MS patient. Demyelination demonstrates a much shorter and more dorsally located lesion in the spinal cord compared to an NMO patient.

**B.** Spinal cord MRI of an NMO patient. The demyelinating lesions extend over three segments of the spinal cord (Images from Helsinki University Hospital MRI-image database).

### 3.10     Treatment and therapeutic options

During the early 19th century, the treatment of ON revolved around placement of solutions in the eye ("collyria"). Various compounds, including spittle, were rubbed in the eye. At the beginning of the 20th century, patients were often treated with sinus surgery or optic canal decompression. The latter was recommended for the treatment of retrobulbar ON as recently as in 1952. Soon after the introduction of corticosteroids in the 1950s, they became the primary treatment of ON and are still the only treatment of scientifically demonstrated value.

According to the ONTT (Beck et al. 1992), oral prednisone was ineffective and promoted ON recurrence. This trial confirmed that intravenous corticosteroids (methylprednisolone 1 g/day) for 3 days followed by prednisone (1 mg/kg body weight/day) for 11 days accelerated visual recovery. Patients treated with this regimen recovered their vision approximately 2 weeks sooner than in those receiving a placebo, but this treatment provided no clear long-term visual benefit. Optic nerve atrophy has been shown to develop following ON and corticosteroids do not have preventive value (Hickman et al. 2003). More recently, these conclusions were confirmed in the Cochrane Database of Systemic Reviews (Gal et al. 2015). The treatment protocol may change in the future due to recent studies, which have shown no clinical disadvantage of using bioequivalent high-dose corticosteroids orally as compared to intravenously (Morrow et al. 2018, Naumovska et al. 2018).

Disease-modifying therapies (DMT) may slow the progression of clinically isolated syndrome (CIS) to definite MS in ON. There are a few significant studies that have reported a risk reduction (10-40%) of this conversion from CIS (30% with ON) to clinically definite MS during a follow up of 3 to 10 years (Comi et al. 2001, Galetta et al. 2001, Comi et al. 2009, Kappos et al. 2016).

### 3.11    Natural course of ON

A recovery of visual acuity to normal or close to normal with time is characteristic of ON. Vision begins to improve after a few weeks and most people regain close to normal vision within a year after an acute ON episode. Although visual acuity in most patients becomes normal, these patients often report a difference how they see with the affected eye compared with the unaffected eye. This can sometimes be confirmed by testing contrast sensitivity and colour vision, both of which may be impaired. OCT may also show changes in RNFL long after an episode of ON, thus explaining the symptoms of the patient (Fisher et al. 2006, Kallenbach & Frederiksen 2007, Longbrake et al. 2016, Levin et al. 2019).

## 4.    Relationship to other demyelinating disorders: MS and NMO

### 4.1    ON in MS

MS is a chronic autoimmune, inflammatory neurological disease of the central nervous system (CNS). MS attacks the myelinated axons in the CNS. The course of MS is highly variable and unpredictable. The disease is often characterized initially by episodes of reversible neurological deficits (such as ON), which in the course of years are often followed by progressive neurological deficits. The disease is diagnosed based on clinical findings and supporting evidence from ancillary testing, such as MRI of the brain and analysis of the CSF (IgG index and OCB especially) (Thompson et al. 2018).

The majority of patients with MS show a relapsing-remitting disease (RRMS) course (85%) and a minority show a primary progressive course (10-15%).

Approximately 15 years from diagnosis, 50% of RRMS patients show a conversion to secondary progression, where inflammatory activity ceases and neurodegeneration takes place. The time to second relapse and the pace of progression of MS are more rapid in women compared to men suffering from RRMS (Achiron & Gurevich 2009).

Immunomodulatory and suppressive treatment in MS targets inflammation and today treatment is initiated soon after the diagnosis of active MS. An interesting uncommon side effect of the modern MS drug fingolimod is macular edema, which is diagnosed with OCT. (Table 2)

**Table 2.** Medications for MS

| Medication | Year of introduction in Finland | Principle of function | Reference |
|---|---|---|---|
| Beta interferons | 1996 | Immunomodulation | Panitch et al. 1987 |
| Glatiramer acetate | 2000 | Immunomodulation | Johnson et al. 1995 |
| Natalizumab | 2006 | Cell traffic inhibition | Miller et al. 2003, Polman et al. 2006 |
| Fingolimod | 2012 | Cell traffic inhibition | Kappos et al. 2010, Cohen et al. 2010 |
| Teriflunomide | 2013 | Immunomodulation | O'Connor et al. 2011 |
| Alemtuzumab | 2013 | Immunodepletion | CAMMS223 Trial Invest. 2008, Cohen et al. 2012 |
| Dimethyl fumarate | 2015 | Immunomodulation | Gold R et al. 2012 |
| Cladribine | 2018 | Selective cytotoxicity | Giovannoni et al. 2010 |
| Ocrelizumab | 2018 | Immunodepletion | Hauser et al. 2017 |

## 4.2    Diagnostic criteria of MS

The latest diagnostic criteria of MS are from 2017. The criteria have evolved somewhat since the previous criteria from 2010 (Polman et al. 2011, Thompson et al. 2018). MS can now be diagnosed after a first clinical attack if paraclinical findings are present. Therefore, in case of an ON, diagnosis of MS may be confirmed already after the first demyelinating episode.

**McDonald 2017**

**Dissemination in Space**

1.  Objective clinical evidence of at least 2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack involving a different CNS site
2.  At least 1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS: periventricular, (juxta) cortical, infratentorial, spinal cord

**Dissemination in Time**

1.  At least 2 attacks separated by a period of at least 1 month
2.  Simultaneous presence of gadolinium-enhancing and nonenhancing lesions at any time
3.  A new T2 and/or gadolinium-enhancing lesion on follow-up MRI, irrespective of its timing with reference to a baseline scan
4.  Demonstration of CSF-specific OCBs (as substitute for demonstration of dissemination of time)

**The key changes of these recent 2017 McDonald criteria are:**

1.  Positive findings of oligoclonal bands in the spinal fluid can substitute for demonstration of dissemination in time.
1.  Both asymptomatic and symptomatic MRI lesions can be considered in determining dissemination in space or time, this does not include MRI lesions in the optic nerve in a person presenting with ON.
2.  Cortical lesions are added to juxtacortical ones in the MRI criteria for dissemination in space.

## 4.3    *ON and the subsequent risk of MS*

Typical ON is frequently but not always associated with MS (Link & Stendahl-Brodin 1983). ON is the first sign of MS in about 20% of people who have MS. The lifetime risk of developing MS after an episode of ON was about 50% before the 2017 McDonald criteria, which allow a rapid diagnosis of MS after the first demyelinating ON episode (ONTT 2008).

In the final follow up of the ONTT from baseline through 15 years, the data showed that the overall risk of MS diagnosis after ON was 30% at 5 years, close to 40% at 10 years, and 50% after 15 years (Optic Neuritis Study Group 2010). The rates were higher for a high-risk group composed of patients who had one or more 3-mm white-matter plaques on MRI at ON onset. Patients with demyelinating lesions on MRI had a 72% risk of developing clinically definite MS within 15 years after a single episode of ON. On the other hand, the patients who had no MRI lesions at the time of ON had an MS risk of only 25% after 15 years follow up (Table 3A) (Optic Neuritis Study Group 2008). Gender differences were large.

A much less known study of ON in Sweden in 1969 to 1981 revealed a 40% MS risk after a follow up of 30 years (Nilsson et al. 2005). Most cases (60%) of MS occurred within 3 years after the onset of ON. About a decade ago, a study from the United Kingdom also confirmed the high risk of MS in patients with CIS suffering from one or more MRI lesions at onset. Of the 140 CIS patients (49% suffering from ON), in those with MRI lesions 82% developed MS in during the follow-up of 20 years, in contrast to only 19% of those without MRI lesions at onset (Table 3B) (Fisniku et al. 2008).

**Table 3.**

**A.** Risk of MS after first ON. Data from the Optic Neuritis Treatment Trial follow-up studies at 5, 10, and 15 years. (Optic Neuritis Study Group 1997, Beck et al. 2004, Optic Neuritis Study Group 2010)

| Demyelinating changes in brain MRI at onset | MS diagnosis after 5-year follow up | MS diagnosis after 10-year follow up | MS diagnosis after 15-year follow up |
|---|---|---|---|
| Yes | 51% | 56% | 72% |
| No | 16% | 22% | 25% |

**B.** Risk of MS after first CIS. Follow up times of 1, 5, and 20 years (Fisniku et al. 2008).

| Demyelinating changes in brain MRI at onset | MS diagnosis after 1-year follow up | MS diagnosis after 5 years follow up | MS diagnosis after 20-year follow up |
|---|---|---|---|
| Positive | 30% | 65% | 82% |
| Negative | 0% | 11% | 21% |

## 4.4    ON in NMOSD

NMOSD, previously known as NMO or Devic disease, is an inflammatory disorder of the CNS. As the diagnostic criteria of NMO have evolved in recent years and considerable variability has been observed in the symptoms and findings of NMO patients, the preferred term for this disease is currently NMOSD. However, the abbreviation NMO is widely used as well.

There are only a few previous studies reporting the prevalence of NMO around the world. In these studies, prevalence of NMO varies greatly, from 0.52 per 100,000 in Cuba (Gabrera-Gomez et al. 2009) to 3.9 per 100,000 in Olmstedt County (Minnesota, USA) (Flanagan et al. 2016).

NMOSD is characterized by severe, immune-mediated demyelination and axonal damage, which predominantly targets the optic nerves and the spinal cord. Hallmark features of NMOSD are acute attacks of severe ON, longitudinally extensive myelitis that often causes limb weakness, sensory loss, and bladder dysfunction with relapsing course. Attacks often occur over days, with variable degrees of recovery during the following weeks and months (Wingerchuk et al. 2006, Wingerchuk et al. 2015).

Approximately one-half of NMOSD patients present with isolated ON, of which about 20% is bilateral. Severe visual loss is a hallmark of ON in NMO. Eighty percent of NMO eyes experience severe loss of visual acuity (VA <0.1) during an acute attack, compared with 36% in MS. Most NMO patients develop unilateral or bilateral functional blindness (VA ≤0.1) at a median of 7.7 years after disease onset (Wingerchuk et al. 1999). The median time from onset of ON to ipsilateral blindness is 2 years and 3 years for contralateral ON. The visual loss in paediatric NMO patients is often more rapid than in adult patients (Collongues et al 2010).

ON of an NMO patient may be distinguished from ON of an MS patient by imaging and functional measures. MRI of an NMO patient is often normal, but may show changes typical of an acute ON. The lesions are often more extensive and likely involve the optic chiasm or adjacent hypothalamus. NMOSD also generally causes more severe visual field defects than ON in an MS patient. Because of its potential to involve the optic chiasm and tracts it may manifest with bitemporal or homonymous hemianopic visual field defects (Khanna et al 2012, Storoni et al 2013, Kim et al 2015).

The discovery of a disease-specific serum NMO-IgG antibody that selectively binds AQP4 has led to increased understanding of this disorder (Lennon et al. 2004, Weinshenker et al. 2006, Paul et al 2007, Waters et al. 2012, Waters et al. 2016). Nevertheless, the cause of NMOSD is still unknown. Similar to MS, an autoimmune inflammatory cascade leads to demyelination and axonal injury through diverse pathways. It has become clear that NMO

and MS are two distinct diseases as many DMTs used in the treatment of MS are either ineffective or even harmful in NMOSD patients (Shimitzu et. al 2008, Lee at al. 2014, Yoshii et al. 2017, Popiel et. al 2018).

CNS involvement outside the optic nerves and spinal cord are observed in patients with NMOSD. Other common symptoms include episodes of nausea, vomiting, hiccups, daytime somnolence or narcolepsy, reversible posterior leukoencephalopathy syndrome, neuroendocrine disorders, and seizures (especially in children) (Wingerchuk et al. 1999, Ghezzi et al. 2004). No clinical features are known that are disease-specific, but some are highly characteristic.

Acute attacks and relapses of NMOSD are treated with intravenous glucocorticoids and sometimes with plasma exchange for refractory or progressive symptoms. Treatment with systemic immunosuppression is the mainstay for prevention of recurrent attacks. Most acute attacks or relapses worsen over days and recover in several weeks to months. Predictors of poor prognosis include the severity of the first attack, the number of relapses within the first 2 years, and older age at disease onset. No controlled trials have evaluated therapies in NMOSD. These therapies are supported by data from observational studies and by clinical experience (Kessler et al. 2016). The most widely used medications for NMOSD have been azathioprine, rituximab, mycophenolate mofetil, and intravenous immunoglobulins (Sellner et al. 2010, Huh et al. 2014, Viswanathan et al. 2015, Damato et al. 2016, Bichuetti et al. 2018). Promising new therapies are emerging in the form of anti-IL-6 receptor, anti-complement, or anti-AQP4-Ab biologicals (Trebst et al. 2014).

## 4.5    *Diagnostic criteria of NMOSD*

The diagnostic criteria of NMO from 2006 were updated in 2015 after data on the development of NMO had been gathered. The more common term for this condition is therefore NMOSD (Wingerchuk 2006, Wingerschuk 2015)

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**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 ON, 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. ON

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 ON: requires brain MRI showing (a) normal findings or only nonspecific white matter lesions, OR (b) optic nerve MRI with T2-hyperintense lesion or T1-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

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### 4.6     *Myelin oligodendrocyte glycoprotein-associated encephalomyelitis*

Recently, next-generation cell-based assays have demonstrated a robust association of autoantibodies to full-length human myelin oligodendrocyte glycoprotein (MOG-ab) with recurrent ON, myelitis and brainstem encephalitis, and acute disseminated encephalomyelitis-like presentations. Most experts now consider myelin oligodendrocyte glycoprotein-associated encephalomyelitis (MOG-EM) a disease entity in its own, immunopathogenically distinct from both classic MS and NMOSD (Jarius et al 2018, Weber et al 2018). The causes for MOG-ab appearance in serum are still unknown, but a connection to infectious mononucleosis has been proposed (Kakalacheva et al 2016). Patients who meet all of the following criteria are diagnosed with MOG-EM (Jarius et al 2018):

1.  Monophasic or relapsing acute ON, myelitis, brainstem encephalitis, or encephalitis, or any combination of these syndromes.

2.  MRI or electrophysiological (VEPs in patients with isolated ON) findings compatible with CNS demyelination.

3.  Seropositivity for MOG-ab as detected by means of a cell-based assay employing full-length human MOG as target antigen.

The treatment of acute attacks of MOG-EM patients with high-dose cortisone is the same as with MS or NMOSD patients. Long-term immunosuppressive treatment with rituximab and azathioprine has emerged as the most effective therapeutic regimen to reduce disease activity in MOG-EM (Borisov et al 2018).

The prognosis of a MOG-EM patient is typically good. There is evidence that it is clearly less disabling than NMOSD in terms of visual function and ambulation (Jurynczyk et al 2017).

## 5.     Pathological considerations

The pathological mechanisms of ON, MS, and NMO are still unknown. Irreversible changes induced during immune or inflammatory attack on myelin during relapses are believed to drive the pathogenesis of MS (Baecher-Allan et al. 2018). Both innate and adaptive immune responses play important roles in the clinical course of MS (Hemmer et al. 2015).

### 5.1     *The role of autoantibodies in ON and MS*

Identification of the target antigens of pathogenic autoantibodies and T lymphocytes is of fundamental importance for understanding the pathogenesis of MS and for the development of personalized treatments for this disease. Forward-translational studies of CD4+ T lymphocytes and reverse-translational studies of CD8+ T and B lymphocytes have led to the identification of many candidate target antigens in patients with MS (Hohlfeld

et al. 2016, Hohlfeld et al. 2016). A unifying antigen, however, has not emerged, which is consistent with the prevailing view that MS is an immunologically heterogeneous disorder (Disanto et al. 2010).

The role of autoantibodies in ON is unknown as well. There is increasing evidence that MOG-ab are associated with the relapsing form of ON (Ramanathan et al. 2014, Chalmoukou et al. 2015, Nakajima et al. 2015, Tsuburaya et al. 2015) and with the prognosis of the visual acuity (Kezuka et al. 2012). These findings are related to a completely new entity, which is called MOG-EM (see chapter 4.6). Seropositivity of AQP4 antibodies has been linked to visual outcomes of ON patients (Kezuka et al. 2012, Martinez-Hernadez et al. 2015). In one study, glycine receptor antibodies (Hutchinson et al. 2008) were evaluated in ON patients but no obvious association was found (Martinez-Hernadez et al. 2015).

## 5.2    *Environmental risk factors of MS*

The main environmental risk factors of MS are vitamin D deficiency in childhood, Epstein-Barr virus (EBV) infection, smoking, overweight in adolescence, exposure to organic solvents, shift work, and birth in springtime (Compston & Coles 2008, Pohl 2009, Handel et al. 2010, Handel et al. 2011, Chan 2012 Degelman et al. 2017, Olsson et al. 2017, McLaughlin et al. 2018, Mowry at al. 2018).

Vitamin D is associated with the development of immunological tolerance (Dankers et al. 2017). Vitamin D deficiency is an epidemiologically well-documented risk factor of MS that appears to be functionally associated with its genetic risk factors. The vitamin D receptor is described to bind more strongly in the promoter region of the HLA-DR15 allele than other alleles and vitamin D particularly increases HLA-DR15 promoter activity (Ramagopalan et al. 2009).

Vitamin D deficiency is also associated with MS through hereditary rickets (OMIM #277440). This rare congenital disease is associated with errors in the vitamin D-activating enzyme (CYP27B1) and is associated with subsequent risk of MS (Torkildsen et al 2008, Ramagopalan et al. 2011). As paediatric patients with this disease generally receive vitamin D replacement therapy since school age, it has therefore been speculated that the time window for MS risk is high during the early years of life (Lee at al. 2013). A correlation with month of birth in MS risk has been observed in several populations; in the northern hemisphere the risk increases in April and May and decreases in October and November (Templer et al. 1992, Willer et. al 2005, Bayes et al. 2010, Saastamoinen et al. 2012, Watad et al. 2017). This is also believed to be related to vitamin D because the umbilical cord blood among newborns in May has been shown to have more T lymphocytes that have undergone "quality control" in the thymus ("thymic emigrants") compared to newborns in November and the measurements correlate with serum vitamin D concentrations (Disanto et al. 2013). Quality control of T lymphocytes occurs in the thymus and eliminates more than

95% of these cells. In particular, T lymphocytes that too strongly recognize self proteins are eliminated. This HLA-mediated detection is most likely sensitized in patients with MS and this process may begin already before birth.

Infectious mononucleosis caused by EBV is associated with clonal proliferation of CD8+ T lymphocytes (Callan et al 1996) and transformation of B lymphocytes into lymphoblasts that contain EBV (Chan et al. 1986). An enrichment of CD8+ T lymphocytes with receptor sequences known to recognize EBV ("public EBV-specific sequences") have been discovered in the cerebrospinal fluid of patients with MS (Lossius et al. 2014). EBV is a herpes virus that infects about 95% of people either asymptomatically in childhood or later as mononucleosis. In particular, EBV infects B cells via the CD21 receptor and remains permanently in a small population of B cells after the virus blocks programmed cell death (apoptosis) by several mechanisms (Price et al. 2014). EBV thereafter remains latent most of the time. However, CD4+ and CD8+ T lymphocyte responses keep viral activation under control. EBV is associated with many lymphoid and epithelial cancers and it was found originally in Burkitt's lymphoma cells (Epstein et al. 1964, Molyneux et al. 2012).

The relationship between EBV and MS is so close that it is difficult to find patients with MS who are seronegative for EBV. In a meta-analysis during the MRI era, only two seronegative patients were found among 1054 patients with MS, whereas 71 seronegative patients were found in a control group of 1703 patients (Ascherio & Munger 2007). EBV seropositivity is already a risk factor for MS, but the risk is significantly higher when the initial infection occured after puberty and caused mononucleosis (Ascherio et al. 2015). It has been suggested that EBV may reside in the central nervous system of MS patients, possibly in B lymphocytes, although this has not been proven (Serafini et al. 2007, Lassmann et al. 2011). Alternatively, autoantigens similar to EBV antigens could act as a stimulator for CD8+ T lymphocytes (Rist et al. 2015).

## 5.3    Development of NMOSD

The cause of NMOSD is unknown. An autoimmune inflammatory cascade leads to demyelination and axonal injury through diverse pathways (Jakob et al. 2013, Manogaran et al. 2016). In NMOSD, demyelination and inflammation involve multiple spinal cord segments and the optic nerves with axonal loss, perivascular lymphocytic infiltration, and vascular proliferation. Necrosis and cavitation typically involve both gray and white matter. Neuroaxonal injury is considered to occur as a secondary consequence of astrocyte damage by AQP4 antibodies and accumulation of damaged mitochondria and transient receptor potential melastatin 4 cation channels in axons (Hokari et al 2016, Kawachi & Lassman 2017). The neuropathologic features of NMOSD at autopsy are those of a much more severe necrotic lesion of the spinal cord rather than incomplete demyelination (Mandler et al. 1993). Whereas MS is believed to be mostly a cell-mediated disorder, the pathophysiology of NMOSD is thought to be mediated relatively more by the humoral immune system

(Graber et al. 2008, Bukhari et al. 2012). Several lines of evidence support an autoimmune pathogenesis for NMOSD. The most important evidence was the identification of a NMOSD disease-specific autoantibody, the NMO-IgG autoantibody, also referred to as the AQP4 antibody (Lennon et al. 2004, Weinshenker et al. 2006).

The difference in the pathogenesis of NMOSD and MS is evident in the unexpected poor therapeutic responses of MS medications in patients with NMOSD (Kimbrough et al 2012, Vodopivec et al. 2015, Kleiter et al. 2016). Common MS drugs, such as natalizumab and fingolimod, have caused fulminant exacerbations of symptoms and MRI findings of NMOSD and termination of these drugs has improved the condition of patients (Min et al. 2012, Yoshii et al. 2016, Yoshii et al. 2017).

### 5.4    *The role AQP4 antibodies in NMOSD*

A specific biomarker of the disease, NMO-IgG, also known as AQP4 antibody, targets the water channel AQP4 located in the foot processes of astrocytes (Jarius et al. 2007, Misu et al. 2007, Popescu et al. 2015). In previous studies, AQP4 antibodies were considered a highly specific test for NMO (85–100%) albeit with lesser sensitivity (32–76%) (Lennon et al. 2004, Waters et al. 2008, Waters & Vincent 2008). Different assay methods for AQP4 autoantibody testing differ in their sensitivity and specificity (Takahashi et al. 2007, Waters & Vincent 2008).

Aquaporins constitute a family of water channels that regulate the transport of water in many organs, including the nervous system (brain and spinal cord), kidney, gastrointestinal tract, secretory glands, inner ear, and muscles (Verkman 2012, Yool &Campbell 2012, Verkman 2013). AQP4 is a homotetrameric protein that is anchored by the dystroglycan protein complex in the plasma membrane of astrocytes and is highly concentrated in their foot processes abutting microvessels, pia, subpia, and subependymal zones (Amiry-Moghaddam et al. 2003). It is also highly expressed in the basolateral ependymal cells and the hypothalamus. AQP4 is involved in the development, function, and integrity of the interface between the brain and blood circulation and between the brain and CSF. AQP4 plays a critical role in the regulation of cell volume and potassium homeostasis. It is involved in development of brain oedema after trauma, water intoxication, ischaemia, infection, and tumours. Serum AQP4 autoantibody titers at the nadir of clinical attacks have been shown to correlate with the length of longitudinally extensive spinal cord MRI lesions (Misu et al. 2009). In addition, serum anti-AQP4 titers in several studies correlate with clinical disease activity; titers drop after immunosuppressive treatment and remain low during remission (Takahashi et al. 2007, Kim et al. 2011, Pellkofer 2011, Isobe 2012, Chanson et al. 2013, Waters et al. 2014). A meta-analysis of 624 AQP4-Ab-positive and 119 AQP4-Ab-negative NMO patients revealed associations between AQP4-Ab seropositivity and visual impairment (Lin et al. 2017). The seropositivity in previous studies for AQP4 antibodies was variable: 11 of 14 in South East Wales, coincidentally the same number in

Northern Japan, and 7 of 9 NMO patients in the Merseyside county of United Kingdom were seropositive (Cossburn et al. 2012, Jacob et al. 2013, Houzen et al. 2017). In Iran, 16 of 33 NMO patients were seropositive (Etemadifar et al. 2012).

# 6. Genetic studies

## *6.1 Developments in genetic methods*

DNA was discovered by the Swiss physician Friedrich Miescher (1844-1895) in 1869 but remained neglected for many decades because proteins, rather than DNA, were thought to hold the genetic blueprint of life. Important new knowledge emerged when Oswald Avery, Colin MacLeod, and Maclyn McCarty demonstrated that purified DNA could change one strain of bacteria into another (Avery et al. 1944). This was the first time that DNA, not proteins as previously widely believed, was proposed as the carrier of genetic information.

In the 1950s the foundation for sequencing proteins was laid by the work of Frederick Sanger, who during his life twice won the Nobel Prize in Chemistry (Sanger 1952). By 1955 he completed the sequence of all amino acids in insulin, a small protein secreted by the islets of Langerhans in the pancreas (Sanger et al. 1955). This provided conclusive evidence that proteins were chemical entities with a specific molecular structure rather than a random mixture of material in a solution. Sanger developed rapid DNA sequencing methods and published a method for "DNA sequencing with chain-terminating inhibitors" (Sanger et al. 1977). At Harvard University Walter Gilbert and Allan Maxam also developed DNA sequencing methods, including one for "DNA sequencing by chemical degradation". They reported in 1973 the sequence of 24 basepairs using a method known as wandering-spot analysis (Gilbert and Maxam 1973). Advancements in sequencing were aided by the concurrent development of recombinant DNA technology, which allowed DNA samples to be isolated from sources other than viruses. Several new methods for DNA sequencing were developed in the 1990s and were implemented in commercial DNA sequencers by 2000. These became known as the "next-generation" or "second-generation" sequencing methods (Metzker 2010, Glenn 2011, Treangen et al. 2011). "Third-generation" sequencing methods, which are also called long-read sequencing, are currently under development (Schadt et al. 2010).

Prior to the introduction of genome-wide association studies (GWAS) around 2000, the most common method of investigation was through inheritance studies of genetic linkage in families (Morton 1955). This approach has proved useful for monogenic disorders. For common, complex diseases, the results of genetic linkage studies are challenging to replicate. The alternative to linkage studies are genetic association studies. Association studies in modestly sized case-control cohorts were performed targeting a few candidate genes. This study type determines if the allele of a genetic variant is found more often than expected in individuals with the phenotype. HLA-DR15 in MS and APOE4 in Alzheimer's

disease were initially discovered by case-cohort candidate gene association studies (Jersild et al 1972, Jersild et al. 1979, de Moerloose et al. 1979, Strittmatter et al. 1993).

In addition to this conceptual framework, a few additional factors enabled GWAS. One was the founding of biobanks that preserve human genetic material. Another was the International HapMap Project that from 2003 onwards identified most of the common single-nucleotide polymorphisms interrogated in a GWAS. The haploblock structure was initially described for chromosome 21 (Patil et al. 2001) and was subsequently utilized by the HapMap project (International HapMap Consortium 2003), which also allowed focus on the subset of SNPs that would describe most of the variation. The first GWAS was conducted in 2005. This study compared 96 patients suffering from AMD with 50 healthy controls. Two SNPs with significantly altered allele frequency between the AMD patients and controls were revealed. These SNPs are located in the gene encoding complement factor H (Klein et al. 2005, Thomas et al. 2005). Since then, a large number of GWAS have been performed in all medical specialties, yielding a remarkable range of discoveries (Visscher et al. 2017).

## 6.2    Genetics of ON and MS

Although MS is not considered a hereditary disease a number of genetic variations have been shown to increase its risk (Ebers et al 1996, IMSGC 2011, Hedström et al 2016, Baranzini & Oksenberg 2017). Some of these risk genes have high levels of expression in microglial cells. The probability of developing MS is higher in relatives of a person with MS and there is a greater risk among those who are more closely related. Of identical twins, both are affected about 30% of the time whereas only around 5% for non-identical twins and 2.5% of siblings are affected. If both parents suffer from MS, the risk of MS in the offspring is 10 times greater than that of the general population (Williams et al. 1980, Kuusisto et al. 2008). The incidence of MS varies widely among different ethnic groups. The lowest incidences are documented among Asians and Africans and highest among Caucasians (Lowis 1988, Rosati 2001, Langer-Gould et al. 2013, Langer-Gould et al. 2014).

The first genetic factor identified to be related to MS was the human leukocyte antigen (HLA) locus in the 1970s (Kissmeyer-Nielsen &Thorsby 1969, Thorsby & Kissmeyer-Nielsen 1969). This locus is located on the short arm of chromosome 6, in a region called the major histocompatibility complex (Patsopoulos et al. 2013). The genes of this region encode highly polymorphic cell-surface glycoproteins that are key components of antigen presentation. HLA class I proteins HLA-A, HLA-B, and HLA-C have multiple alleles in humans and present antigens to the CD8+ T lymphocytes and in some natural killer cells (Natarajan et al. 2018). HLA class II proteins HLA-DR, HLA-DQ, and HLA-DP are also highly polymorphic and present antigens to CD4+ T lymphocytes. Virtually all autoimmune diseases are associated with HLA and differences associated with genetic load or gender have been reported, highlighting the complexity of how the HLA locus exerts its influence

on MS (Apanius et al 1997). The new genomic tools available in recent decades confirmed the association of the HLA class II haplotype DRB1*15:01–DQA1*01:02–DQB1*06:02 with MS (Barcellos et al. 2006, Kollaee et al. 2012, Cocco et al. 2012, Hollenbach & Oksenberg 2015). Thirty-five years after the first report on the role of the HLA region in MS, GWAS identified genetic risk factors for MS outside of the HLA region. These were variants in the cytokine receptor genes interleukin-2 receptor alpha (*IL2RA*) and interleukin-7 receptor (*IL7R*) (Lundmark et al. 2007, Kreft et al. 2012, Liu et al 2017). Five important genetic factors have also been identified in multiple families by linkage and in family-based and case-control association analyses in the Kyrönmaa region in Finland, namely HLA, MBP, STAT3, IL7R, and C7/FLJ40243 (Tienari et al. 1992, Tienari et al. 1993; Kuokkanen et al. 1996; Kuokkanen et al. 1997; Pihlaja et al. 2003, Kallio-Laine et al. 2009, Jakkula et al. 2010, IMSGC 2013 and 2017). MBP and STAT3 genes are also implicated in cancer. MBP is associated with childhood leukemia and non-Hodgkin's lymphoma (Han et al. 2010, Ouyang et al 2016). These suggest that MS and haematologic cancers may have common background mechanisms. STAT3 regulates cell proliferation against programmed cell death and activation of the STAT3 signaling pathway is implicated in many types of cancer (Johnson et al. 2018). Activating somatic STAT3 mutations have been found in CD8+ T lymphocytes in leukemia and in some patients with MS (Koskela et al. 2012, Andersson et al. 2013, Rajala et al. 2015, Valori et al. 2017). It is of interest that HLA-A2, which is associated with protection from MS, is also associated with reduced risk of EBV-positive Hodgkin's lymphoma (Niens et al 2007, Jones et al 2016).

There are no known monogenic forms of MS. Some genetic diseases like LHON (Sadun et al. 2002, DeBusk et al 2018) and OPA1 disease, which cause optic neuropathy as well, (Sitarz et al. 2012, Yu-Wai-Man et al. 2016), mimic ON and MS.

## 6.3    *Genetics of NMO*

Although an HLA association has been demonstrated, no specific NMO genes have been identified thus far. A small percentage of people with this condition have a family member who is also affected, which indicates that one or more genetic changes increase susceptibility (Matiello et al. 2010). The inheritance of NMO is considered to be complex and many environmental and genetic factors are involved in its development. In Japan and China, NMO is associated with HLA-DPB1*0501 allele (Matsushita et al. 2009, Wang et al. 2011) and in Brazil with HLA-DRB1*03:01 (Alvarenga et al. 2017). A recent genetic study from the USA suggests that distinct genetic variants in the MHC region (HLA-DRB1*03:01 and complement C4 gene low copy number haplotype) contribute to the aetiology of NMO and that NMO is genetically more similar to systemic lupus erythematosus than to MS (Estrada et al. 2018). Preliminary data on other associations have also been reported, but these findings are still uncertain (Matiello et al. 2011, Wingerchuck and Weinshenker 2014).

# 7.     Aims of the study

As the incidence of demyelinating diseases (particularly MS) are high in Finland, we were interested in studying the natural course and epidemiology of ON in our healthcare district. The differential diagnosis of ON is often considered challenging. Therefore, we sought to determine how often the initial diagnosis is correct and if other factors should be considered to improve the diagnostic accuracy of ON in the future.

Very little is known about the genetics of NMO, apart from its association with the HLA system (Ono et al. 1998, Brum et al. 2010) (Table 6). Although the prevalence of NMO in Finland is low, the Finnish genetic background is suitable for studying rare diseases like NMO. Finland has been relatively isolated for centuries and therefore the Finnish population has a relatively small number of founders. If there are rare variants with a strong genetic effect, these would be more easily detected in the Finnish population than in more mixed populations. Before this study, only a few patients with NMO had been treated in our hospital district. Some of these patients were considered for years to have a severe variant of MS until the discovery of AQP4 antibodies. The first symptom of NMO is often uni- or bilateral ON that often poorly recovers. Therefore, I considered it would be of clinical relevance for early diagnosis and treatment to identify NMO patients already at the onset of the first symptoms.

The present study was therefore undertaken to achieve the following aims: to determine the incidence of ON in Southern Finland and to identify the diagnostic challenges associated with acute idiopathic ON (Study I); to identify the symptoms present in an unselected ON cohort and the factors that modulate the prognosis of ON (Study II); to assess the utility of AQP4 antibody tests in diagnostics of NMO in patients with ON in Finland (study III); and to identify rare genetic variants that predispose to NMO in Finland (Study IV).

# 8.     Subjects and methods

## 8.1     *Patient populations in each study*

### 8.1.1     Studies I and II

All 291 patients referred to the Department of Ophthalmology, Helsinki University Hospital, Finland between May 1, 2008 and April 14, 2012 (a period of 47.5 months) with symptoms suggestive of acute or subacute ON were eligible. The hospital receives virtually all patients with an acute ON that live 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 the study period (28% of the population of Finland, 5.4 million in 2011). Therefore, the sample was essentially population-based in the geographic catchment area without any administrative selection criteria.

### 8.1.2 Study III

The subjects were the same as in study I (7.1.1) except that 9 more patients were included in this study who were later excluded from studies I and II because of clerical errors (miscoded diagnosis or personal identification error).

### 8.1.3 Study IV

Two patients with NMO were incident cases identified in my previous studies and 3 additional NMO patients were identified by reviewing the patient databases of the Departments of Neurology and Ophthalmology in the Helsinki University Hospital from 2008 to 2013.

## 8.2 Clinical laboratory examinations

A battery of blood tests was performed in all patients as part of an ongoing clinical trial (MINOPTIC, https://www.clinicaltrialsregister.eu/ctr-search/search?query=minoptic): ESR, full blood count, CRP, calcium, sodium, potassium, albumin, creatinine, alkaline phosphatase, γ-glutamyltransferase, alanine aminotransferase, glucose, thyroid stimulating hormone, *Borrelia burgdorferi* antibodies, AQP4 autoantibodies, and pregnancy test (for women). All tests except for AQP4 autoantibodies were performed in the clinical laboratory (HUSLAB) of the Helsinki University Hospital. AQP4 autoantibodies were quantified in the laboratory of prof. H.P. Seelig, Karlsruhe, Germany, using an in-house radioimmunoprecipitation method with *in vitro* transcribed and translated $^{35}$S-methionine labelled human AQP4 as antigen. An AQP4 index >15 was considered positive, 10 to 15 borderline, and <10 normal (Paul et al. 2007).

## 8.3 Imaging studies

MRI of the brain and the orbits was performed within 24 hours after hospital admission, 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 acute phase for various reasons: in 41 patients MRI had been performed recently as a part of MS follow up, 4 patients were referred immediately to a neurologist before MRI screening, and 5 patients had other reasons (e.g. claustrophobia). A spinal MRI was obtained in all patients with spinal cord symptoms or positive or borderline AQP4 autoantibody index.

## 8.4 Genetic methods and bioinformatics

In study IV, exome (Roche Nimblegen v3, 64 Mb), HLA region (Roche Nimblegen HLA, 5 Mb), and a custom selection of regulatory regions exhibiting open chromatin/DNAse I-hypersensitive sites in immune cells (64 Mb) were captured from genomic DNA using a custom-designed SeqCap kit (Roche NimbleGen Inc., Madison, Wisconsin, USA). The

non-coding sequences targeted in addition to exome represent the top 1 percentile of open chromatin replicated in multiple samples of each immune cell type (n=17) by NIH RoadMap Epigenomics (PMID: 25693563). Next-generation sequencing with an average coverage depth of 25X was performed using an Illumina HiSeq2500 instrument at McGill University and Génome Québec Innovation Center, Montreal, Canada. Reads from the HiSeq output were mapped to the reference genome (hg19) using the Burrows-Wheeler Aligner (Li et al. 2009) and variants were called with the Genome Analysis Toolkit (McKenna et al. 2010). Non-synonymous variants in coding regions that showed a frequency of 0.01 in the 1000 genomes (1000 Genomes Project Consortium), ExAC (exac.broadinstitute.org), and Finnish SISU (sisu.fimm.fi) population exome databases were considered for further analysis. Non-coding variant frequencies were estimated based on the 1000G database and an in-house database of McGill University Genome Centre. Systematic errors were filtered using the Genome Analysis Toolkit VQSR method and by comparison with control samples sequenced at the same time. We searched the NMO patient data for rare variants by the following: (i) shared exonic non-synonymous variants, (ii) shared non-coding variants, (iii) shared non-coding variants with a high CADD score suggesting functional effect (Kircher et al. 2014), and (iv) genes with clustering of any non-synonymous variants. HLA typing (A, B, C, DQA1, DQB1, and DRB1 genes) was performed by using the software PHLAT (Bai et al. 2014). HLA-DPB1 typing was performed separately using sequence-specific primers (SSP: Olerup SSP, Stockholm, Sweden).

## 8.5   *Statistical methods*

In Study 1 and in Study 3, confidence intervals and positive and negative predictive values for the development of MS were determined using SPSS for Windows, version 21.0 (IBM Corp, Armonk, NY, USA).

In Study 2, statistical analysis was performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp, Armonk, NY, USA) and Stata: Release 15 (College Station, TX: StataCorp LLC, USA). A binominal test was used to test whether recurrent ON occurred equally in the same or the other eye. Mann-Whitney $U$ test and non-parametric test for trend were used to compare continuous variables between unordered and ordered groups, respectively. Fisher's exact test and Jonckheere-Terpstra test were used to compare categorical variables in unordered and doubly ordered contingency tables, respectively. Walter-Elwood test (Walter 1977) was performed for monthly distribution of patients and the linear regression for the change of visual acuities. Statistical significance was set at the 5% level.

# 9. Results and discussion

## 9.1. Study population

Altogether 291 cases were reviewed and 184 fulfilled the inclusion criteria of ON. A flowchart of the study population is shown in Figure 13. Most patients (63%; 95% CI 57-69) were indeed diagnosed with ON but 37% were diagnosed with another condition. These 107 patients with disease mimicking ON had 35 different diagnoses; the most common were NAION, anterior uveitis, and dry eyes. It is not surprising that NAION patients are mistakenly diagnosed as ON since the clinical findings initially are often quite similar, except that NAION patients are usually older and the onset of symptoms is more sudden. Patients with their first anterior uveitis are often young and the clinical findings may be minor; therefore it is possible that the patient is at onset diagnosed with ON. A larger than anticipated number of diseases that at onset mimicked ON was found, which is a reminder of the challenges associated with ON diagnosis at symptom onset. A recent study from the USA also revealed the challenges in ON diagnosis, as the majority of patients referred for ON were diagnosed with a disease other than ON. In this material NAION was also one of the most common diagnoses (Stunkel et al. 2018).

## 9.2 Distribution of ON cases by underlying disorder

Most patients with ON had their first ON (67%) and approximately one third had a previous diagnosis of MS (Figure 13). As NMO is rare in Finland only 2 patients were diagnosed with NMO, both with their first ON. Three patients (1.6%, 95% CI 0.16-3.0) had bilateral ON; 2 of them had MS and 1 was diagnosed with NMO. In our study, MRI (1.5 or 3 Tesla) was performed on 135 (73%) patients. Most of the patients screened with MRI (81%) had demyelinating lesions in brain MRI, which is apparent since ON in most cases is related to demyelinating diseases. One of the most interesting findings was in the 6 patients who had intracranial expansions in MRI at the onset of suspected ON. Most of them were subsequently operated on by neurosurgeons. This observation emphasizes the importance of performing MRI upfront. The same observation was reported in a recent study from the USA where 4% of suspected ON cases were diagnosed as optic sheath meningioma (Stunkel et al. 2018). There are also reports of optic nerve lymphoma and optic nerve sheath melanoma cases as serious compressive lesions that mimic ON (Kim et al. 2015, D'souza et al. 2017). Sarcoidosis may also affect the optic nerve, but most of the ocular involvement is related to uveitis (Karma & Mustonen 1985, Rothova 2000). The presence of any demyelinating lesions was a strong predictor of MS, as 54% of the patients with demyelinating lesions in their MRI versus 5% of patients without demyelinating lesions 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 (Ransohoff et al 2015, Spelman et al. 2017), a MRI scan should be considered in the routine diagnostic work-up of ON to facilitate early diagnosis and early treatment of MS.
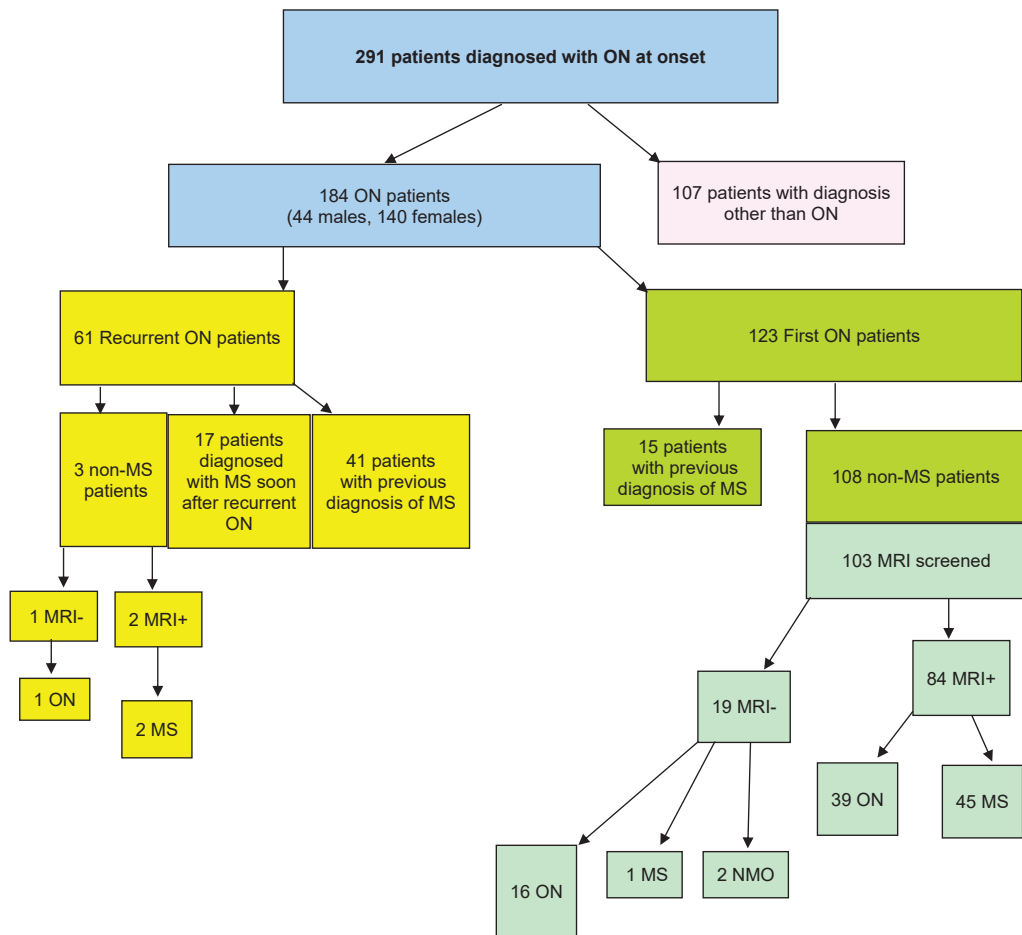
**Figure 13.** Flowchart with 291 suspected ON patients according to their relation to disease.

## *9.3     Incidence of ON*

In this data the estimated crude incidence of ON is now slightly higher in Southern Finland Uusimaa county than previously reported (Kinnunen 1983). The crude incidence was 3.0 (95% CI 2.8-3.3) per $10^5$ (females, 4.6 per $10^5$; males, 1.4 per $10^5$) compared to the earlier incidence estimate of 2.4 per $10^5$ in Southern Finland (Kinnunen 1983) (Table 4).

**Table 4.** Optic neuritis incidence per $10^5$ in Southern Finland Uusimaa and Western Finland Vaasa counties.

| | Study period | Mean population/ year | Patients with ON (n) | Crude incidence per $10^5$ with 95% confidence intervals (CI) | | |
|---|---|---|---|---|---|---|
| | | | | Total | Male | Female |
| Finland (Uusimaa County) (present study) | 2008-2012 | 1.5 million | 184 (44 males, 140 females) | 3.0 (95% CI 2.8-3.3) | 1.4 (95% CI 1.0-1.8) | 4.6 (95% CI 3.9-5.4) |
| Finland<br>- Uusimaa County<br>- Vaasa County<br>(Kinnunen 1983) | 1970-1978 | 1.1 million<br>430,000 | 227 (67 males, 140 females)<br>88 (33 males, 55 females) | 2.4 (95% CI 2.1-2.7)<br>2.3 (95% CI 1.8-2.8) | 1.5 (95% CI 1.2-1.8)<br>1.8 (95% CI 1.2-3.4) | 3.2 (95% CI 2.7-3.7)<br>2.8 (95% CI 2.0-3.6) |

The present incidence is more reliable as some mimickers of ON can be differentiated from ON (Kupersmith et al. 2002, Chan et al. 2012, Berg et al. 2015, Fard et al. 2018). In the previous study in Finland from the 1970s, MRI and most of the other ancillary methods were not available (Kinnunen 1983). It is likely that the incidence of ON has increased slightly more than the figures directly indicate, probably because of the lower number of false-positive diagnoses in the present study. In the 1970s catchment, most patients with ON were referred to their local central hospital. While this happens today as well, more and more patients are evaluated in private-sector hospitals, which may also decrease the incidence of ON in this study.

On the other hand, the development of the health care system in Finland may today more often find patients with ON than in the previous study. Today people may also more actively search for medical advice even with less severe symptoms, which may also increase the incidence.

The incidence rate of ON varies widely around the world. The high incidence of 5.4 per $10^5$ in a recent study from Spain (Martinez-Lapiscina et al. 2014) suggests that the incidence of ON is rising. The population of that study was quite small (300,000) and the study area was limited to a small region in Spain (Barcelona area); those figures are thus not quite comparable to other studies and are subject to more random variations from year to year. Northern Europe and Sardinia in Italy (Congia et al. 2012) are known to be areas with high incidence of MS. As ON is often related to MS, the lower incidence of ON in these areas compared to the Barcelona area is perhaps surprising. The well-known observation that MS

is quite rare in Asia is well correlated with the low incidence of ON in Singapore (Lim et al 2009).

## 9.4    Age and sex

The mean age of patients with ON in this study was 34 years (range 15-61 years) and about three quarters (76%) of the patients were female (Figure 14). A trend for a similar unequal gender distribution has been shown in previous ON studies. The mean age of patients with ON was also comparable to previous findings (Optic Neuritis Study Group 1997, Jin et al. 1998, Wakakura et al. 1999, Zhang et al. 2007, Lim et al. 2008, Soelberg et al 2017).
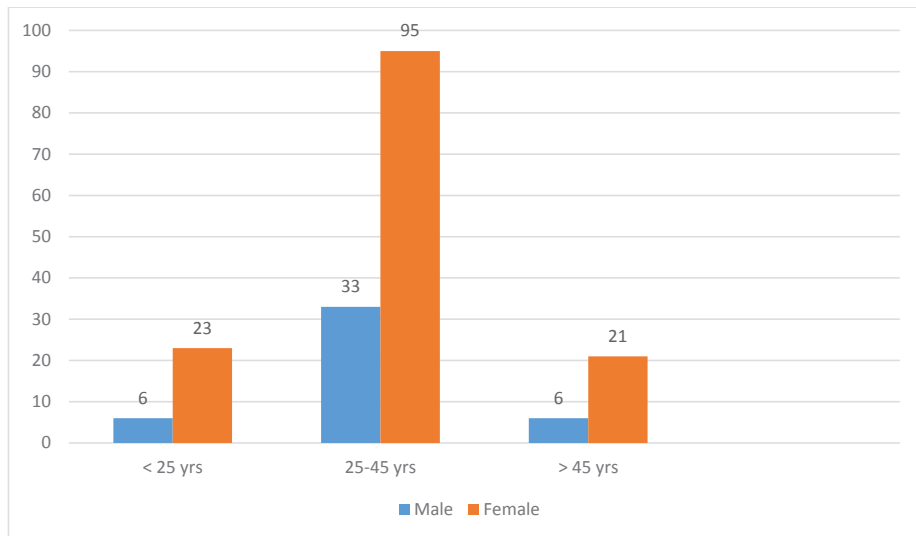


**Figure 14.** Gender distribution of patients with ON (n=184) in three age groups.

## 9.5    Seasonality

The incidence of ON was analysed by month and by season (Q1= January-March, Q2=April-June, Q3=July-September, Q4=October-December). The quarterly incidence of ON was highest in Q2 and lowest in Q4. The Q2 versus Q4 comparison revealed an odds ratio of 2.0 for Q2 (95% CI 1.09-3.68, p=0.030, Fisher's exact test), which is similar to data from Sweden (Jin et al. 2000). Using the Walter-Elwood test (Walter 1977), we observed a significant difference in monthly distribution of ON patients (p=0.026).

## 9.6    Clinical findings

### 9.6.1    Visual acuity

The median baseline BCVA of all ON patients at time of ON diagnosis was 0.2 (range CF-1.0) on a Snellen chart. Evolution of BCVA was analyzed in 132 (72%) patients, who

were reviewed ≥30 days after onset (median 38 days). Median BCVA in these 132 patients was 0.4 at the time of diagnosis and 1.0 at time of review. Recovery was relatively good in the majority of patients; at the time of review, 82% (n=108) and 70% (n=92) achieved a BCVA of ≥0.5 and ≥0.8, respectively. Only 10% had poor recovery (BCVA ≤0.1) at review.

### 9.6.2    Prognostic factors

We observed that visual acuity at review was poorer among patients with swelling in optic nerve (microscopic examination) (p=0.033, Mann-Whitney *U* test) and among patients with demyelinating MRI lesions in the optic nerve (p=0.049, Mann-Whitney *U* test). While seropositivity of AQP4 antibodies has been linked to visual outcomes of ON patients (Kezuka et al. 2012, Martinez-Hernadez et al. 2015), this was not observed in the studies presented here.

### 9.6.3    Pupillary function and optic disc

RAPD was positive in most (n=132, 76%) of the tested patients. The interquartile range of visual acuity among RAPD-negative patients was 0.1 to 0.6. Patients with recurrent ON (n=61) were excluded from RAPD analysis because RAPD is an unreliable sign if the relapse affected the previously unaffected eye. Of the 61 patients with a previous history of unilateral ON, recurrent ON was found in the same eye in 64% (95% CI 58-70) and in the other eye in 36% (95% CI 30-42) of patients. As the sample size was small, we did not have enough evidence to conclude that this distribution deviated from chance (p=0.088, binominal test).

Optic disc swelling, which is sometimes considered a typical symptom of ON, was found in only 21% of patients. Instead, more common findings were colour vision impairment (75%, 95% CI 70-80) and pain with eye movements (65%, 95% CI 60-70).

### 9.6.4    Clinical chemistry

A battery of blood tests was performed in all patients because of an ongoing clinical trial. Positive AQP4 antibodies were found in 3 patients, but only 1 was diagnosed with NMO. Although 10% of patients had a positive IgG titre for *Borrelia burgdorferi*, this seroprevalence is similar to that of the general population of Southern Finland (Oksi et al. 2013). MOG antibodies were not assessed but would have been a useful addition to the otherwise comprehensive laboratory package, as it is known that patients with NMOSD with MOG antibodies have distinct clinical features. MOG antibodies are also included in the revised diagnostic criteria of NMO from 2015 onwards (Kitley et al. 2014, Sato et al. 2014).

### *9.7.      NMO in Southern Finland and specificity of AQP4 antibodies*

We measured the AQP indexes of consecutive patients referred between May 1, 2008 and April 14, 2012 (a period of 47.5 months) with symptoms suggestive of acute or subacute ON. A positive AQP4 autoantibody index was found in 3 patients (1.6%, 95% CI 0.3-4.5) and a borderline index in 10 (5.2%; 95% CI 2.5-9.4) patients.

Of the 3 AQP4 index-positive patients, 1 patient had unilateral ON and a previous diagnosis of MS. One patient had unilateral ON and several demyelinating lesions in MRI, fulfilling three of the four Barkhof's criteria at the time of first examination; this patient was diagnosed with MS 1 month later. A third patient had definite NMO according to the diagnostic criteria valid at the time (Wingerchuk et al. 2006). One additional patient was also diagnosed with NMO but had a normal AQP4 autoantibody index. This patient fulfilled all the absolute and supportive diagnostic criteria of NMO except for the increased AQP4 index.

We found only 2 patients that fulfilled the diagnostic criteria (valid at that time) of NMO, which confirms the rarity of NMO in Finland. The positive predictive value of the AQP4 index for NMO was 1/3 and its sensitivity was 1/2 in this cohort, which shows that the AQP4 antibodies test is not specific or sensitive in the Finnish population (Table 5). Therefore, it is advisable to perform remeasurements of AQP4 antibodies in patients with suspected NMO suspects. It is important to note that a negative AQP4 index does not exclude an NMO diagnosis.

The diagnostic criteria of NMO have significantly evolved and, therefore, a new study according to the revised diagnostic criteria from 2015 would probably increase the prevalence of NMO/NMOSD in Finland. These new criteria are not as strict as the previous criteria and thus more patients would be diagnosed with NMOSD today.

**Table 5.** Distribution of ON patients according to their AQP4-antibody status.

| Patient group | AQP4 positive patients n=3 | AQP4 negative or borderline patients n=188 |
|---|---|---|
| NMO patients n=2 | 1 | 1 |
| MS patients n=66 | 1 | 65 |
| ON patients n=123 | 1 | 122 |

## 9.8 **Exome and regulatory region sequencing in NMO**

In exome sequence analysis, 185 to 305 rare non-synonymous variants with a population frequency <0.01 was observed in each of 5 NMO patients. None of these variants was found in all 5 patients. Four rare non-synonymous variants were shared by 2 patients each; these were found in four genes (*C3ORF20, PDZD2, C5ORF47,* and *ZNF606*). The *C5ORF47* variant was shared by two AQP4 seropositive patients; otherwise the patients that shared rare variants were discordant for the AQP4 autoantibody index. The *PDZD2 V1121M* variant was the only variant that was predicted as deleterious by both PolyPhen-2 (genetics. bwh.harvard.edu/pph2/) and SIFT (sift.jcvi.org) programs. Two additional *PDZD2* variants were found (both predicted as non-deleterious): patient 2 had a D6Q variant (predicted deleterious) and patient 4 had a second variant *T56M* (predicted non-deleterious). Patient 3 carried three rare variants in the four genes shown; patients 3 and 4 shared two rare variants of these four genes. We did not find rare variants in the non-coding sequence (frequency <0.01) shared by all patients. Two single-nucleotide variants with a high CADD score of 25 were shared by two AQP4-seropositive patients (patients 1 and 2): rs13029421 in an intron of the *PLB1* gene and rs12516549 between *LOC340074* and *SLC25A48* (frequencies 0.015 and 0.010 in 1000G) (Table 7).

One of the AQP4 autoantibody-positive patients carried the proposed risk allele DPB1*0501 (Table 8). No non-synonymous variants were found in the AQP4 gene, a proposed genetic risk factor of NMO.

**Table 6.** HLA associations of NMO patients in other studies.

| Risk allele (R)/protective allele (P) | Population | Reference |
|---|---|---|
| HLA-DRB1*03 (R) | Brazilian mulatto | Brum et al 2010 |
| HLA-DRB1*03 (R) | French Afro-Caribbean | Deschamps et al 2011 |
| HLA-DRB1*04.04 (R) | Muslim Arab Israeli | Brill et al 2016 |
| HLA-DRB1*10:01 (R) | Muslim Arab Israeli | Brill et al 2016 |
| HLA-DRB1*07 (P) | Muslim Arab Israeli | Brill et al 2016 |
| HLA-DQB1*02:02 (P) | Japanese | Brill et al 2016 |
| DRB1*09:01 (P) | Japanese | Yoshimura et al 2013 |
| HLA-DPB1*05:01 (R) | Japanese | Matsushita et al 2009 |

**Table 7.** Genetic variants found in the NMO patients in this study.

**A.** All non-synonymous variants.

| Population frequency | Pt 1* | Pt 2* | Pt 3* | Pt 4 | Pt 5 |
|---|---|---|---|---|---|
| ≤1 | 8095 | 7977 | 8422 | 8291 | 7782 |
| ≤0.1 | 921 | 835 | 929 | 961 | 875 |
| ≤0.01 | 241 | 187 | 225 | 185 | 305 |
| ≤0.001 | 115 | 66 | 86 | 60 | 179 |
| ≤0.0001 | 57 | 31 | 37 | 33 | 81 |
| 0 | 38 | 20 | 23 | 22 | 31 |

**B.** Shared non-synonymous rare variants

| Gene | Variant (freq <0.01) | AA change | Finnish population frequency | Pt 1* | Pt 2* | Pt 3* | Pt 4 | Pt 5 |
|---|---|---|---|---|---|---|---|---|
| *C3ORF20* | rs35363400 | F582L | 0.003024 | X | | | | X |
| *PDZD2* | rs149535005 | V1121M | 0.003175 | | other | X | X+ other | |
| *C5ORF47* | rs115473626 | P81L | 0 | X | | X | | |
| *ZNF606* | rs139131343 | V40M | 0.001064 | | | X | X | |

**C.** Shared non-coding rare variants with high CADD score

| Gene | Variant | AA change | Finnish population frequency | Pt 1* | Pt 2* | Pt 3* | Pt 4 | Pt 5 |
|---|---|---|---|---|---|---|---|---|
| *PLB1* | rs13029421 | intronic | 0.015 | X | X | | | |
| *Intergenic* | rs12516549 | | 0.01 | X | X | | | |

*AQP4 autoantibody-positive patient.

The *PDZD2* variant was the only rare shared variant that was predicted as deleterious by SIFT and PolyPhen-2. Other *PDZD2* variants were found in Pt 2 (rs116598198 D6Q, population frequency approximately 0.02) and Pt 4 (rs145138976 T56M, population frequency approximately 0.03). The *C5orf47* variant, while not found in the ExAC Finnish population, has a frequency of approximately 0.02 in the African population.

**Table 8.** HLA typing of NMO patients.

| Patient | Locus | Allele 1 | Allele 2 |
|---------|----------|----------|----------|
| 1 | HLA_A | 02:01 | 68:01 |
| | HLA_B | 15:10:01 | 44:02:01 |
| | HLA_C | 05:01:01 | 16:02:01 |
| | HLA_DQA1 | 03:01:01 | 03:03:01 |
| | HLA_DQB1 | 03:01:01 | 03:01:01 |
| | HLA_DRB1 | 04:03:01 | 08:01:04 |
| | HLA_DPB1 | 02:01 | 03:01 |
| | | | |
| 2 | HLA_A | 01:01 | 02:01 |
| | HLA_B | 37:01:01 | 56:01:01 |
| | HLA_C | 01:02:01 | 06:02:01 |
| | HLA_DQA1 | 01:03:01 | 03:01:01 |
| | HLA_DQB1 | 03:02 | 06:03 |
| | HLA_DRB1 | 04:01:01 | 13:01:01 |
| | HLA_DPB1 | 04:01 | 04:01 |
| | | | |
| 3 | HLA_A | 24:02:01 | 31:01:02 |
| | HLA_B | 07:02:01 | 18:01:01 |
| | HLA_C | 07:01:01 | 07:02:01 |
| | HLA_DQA1 | 01:02:01 | 01:02:01 |
| | HLA_DQB1 | 06:02:01 | 06:02:01 |
| | HLA_DRB1 | 15:01:01 | 15:01:01 |
| | HLA_DPB1 | 04:01 | ***05:01*** |
| | | | |
| 4 | HLA_A | 03:01:01 | 68:01:02 |
| | HLA_B | 07:02:01 | 35:01:01 |
| | HLA_C | 03:03 | 07:02 |
| | HLA_DQA1 | 01:02:01 | 04:01:01 |
| | HLA_DQB1 | 04:02:01 | 06:02:01 |
| | HLA_DRB1 | 08:01:03 | 15:01:01 |
| | HLA_DPB1 | 02:01 | 03:01 |
| | | | |
| 5 | HLA_A | 01:22N | 32:01:01 |
| | HLA_B | 44:02:01 | 47:01:01 |
| | HLA_C | 05:01:01 | 06:02:01 |
| | HLA_DQA1 | 01:01:01 | 03:03:01 |
| | HLA_DQB1 | 03:01:01 | 05:01:01 |
| | HLA_DRB1 | 01:01:01 | 04:01:01 |
| | HLA_DPB1 | 04:01 | 04:02 |

* Only one previously reported HLA risk allele found

## *9.9    Limitations of the studies*

### 9.9.1    Study I

The diagnostic criteria for ON are not entirely clear and straightforward. Therefore, diagnosing ON is sometimes quite challenging. As the patients were consecutive patients

with suspected ON and consulted with different resident doctors, the experience and skills of the resident doctors varied thus leading to broad range of diagnoses. This may explain the large number of ON-mimicking diseases considered first as suspected ON. The results might have been more specific if this study was performed in a prospective setting and the same researcher consulted with all patients. Some patients with ON probably had only minor symptoms that improved rapidly and therefore these patients never consulted an ophthalmologist. Some patients only met their private ophthalmologist and when their symptoms did not qualify for i.v. corticosteroid treatment they were not referred to my hospital. For these reasons, the incidence of ON may be somewhat higher than observed in this study. 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 a lower incidence of MS.

### 9.9.2    Study II

In addition to the limitations of study I, some conclusions may be weakened due to the varying follow-up times between patients. All examinations were not performed on every patient.  In practice, all patients with ON in my hospital are reviewed 1 month from the onset. However, due to patient- and physician-related matters, the control times often slightly varied and some patients never returned for review. Most patients had their brains and orbits screened with MRI 24 hours after first appointment at my hospital. Some patients with MS had been screened recently in the Department of Neurology and some patients refused MRI (because of e.g. claustrophobia). The timing of MRI was therefore not equal in all patients.

### 9.9.3    Study III

The laboratory test to diagnose AQP4 antibodies has evolved. The test we used, the radioimmunoprecipitation method measured in the laboratoty of H.P Seelig in Karlsruhe, Germany, is not considered the most specific and sensitive test today. At the time when the patient data were examined (2008-2012), the knowledge of NMO was quite incomplete. Therefore, it is possible that some AQP4 autoantibody-negative patients with NMO were still diagnosed and treated as MS patients. Because the number of patients with NMO was low (n=2) in this study, the specificity and sensitivity values are only rough estimates.

### 9.9.4    Study IV

We found only 5 NMO patients from Southern Finland during the study period. Since the number of exome-sequenced patients was low, we were only able to detect very strong genetic factors linked to NMO. As knowledge on the heterogeneity of NMO has increased in recent years, it is anticipated that the number of NMO patients must be much higher to find important genetic variants. Due to the heterogeneity of NMO (e.g. AQP4-positive versus -negative patients), future genetic studies probably should concentrate on certain subgroups of NMO.

## *9.10  Future directions for research*

### 9.10.1  ON

The diagnosis of ON is clinical and no universal diagnostic criteria are available. It is therefore challenging to compare different ON studies. The evolution of computerized imaging methods (e.g. OCT) may set better standards for the diagnosis of ON. In retrobulbar ON, the optic disc may not show any signs of ON. Therefore, an easy and accessible screening method for the retrobulbar part of the optic nerve would also bring important objective data. No laboratory tests are specific for ON. A reasonably specific antibody found in ON patients, such as that for NMO patients, would be useful. However, it may be unlikely that such an antibody will be found as ON most probably is not an antibody-mediated disease like NMOSD.

Genetic studies in some other autoimmune diseases, like rheumatoid arthritis, have found weak-to-modest predictive value with regards to patient treatment (Plant et al. 2014, Cherlin et al. 2018). In MS, some pharmacogenomics findings regarding the generation of IFNβ neutralizing antibodies, anaphylactic reactions in natalizumab treatment, glatiramer acetate treatment response, and non-response to IFNβ have been observed (de la Hera et al. 2014, Esposito et al. 2015, Ross et al. 2017, Buck et al. 2018).

Future genetic studies of ON may also reveal information on possible genes that specifically trigger ON, modify its outcome, or predict treatment response. Genetic studies may lead to the discovery of new treatment targets or pathways as has been shown in SLE (Rankin et al. 2013, Julia et al. 2018), which may lead to new treatment possibilities.

Currently, the only known medication for acute ON is still intravenous high-dose corticosteroids. The method of administration may change in the future, as some recent studies have revealed that bioequivalent oral high-dose corticosteroids compared well with intravenous administration (Morrow et al. 2018, Naumovska et al. 2018). New medications for ON have been studied but no prominent discoveries have been made. However, the evolution of medical treatment in closely related MS has advanced significantly recently. While there is some evidence that the human monoclonal antibody, opicinumab, may promote the recovery of the VEP of patients with ON, more data on that preliminary observation is needed (Cadavid et al. 2017, Cadavid et al. 2018, Klistorner et al. 2018). Erythropoietin may have also some potential in the treatment of ON, as some indication of its neuroprotective mechanisms was documented a few years ago.  Erythropoietin has shown neurotrophin-like properties in various models of brain injury. In an animal model of ON, erythropoietin was particularly effective when given in combination with methylprednisolone (Sühs et al. 2012). A new larger study of erythropoietin in the treatment of ON is ongoing (Diem et al. 2016). We have studied minocycline, a tetracycline-derivative antibiotic, in the treatment of acute ON in our clinic. Previously, minocycline has shown promising results in MS-related studies. In rodent autoimmune encephalomyelitis, a model

of MS, minocycline was found to decrease the infiltration of T cells into the central nervous system (Popovic et al. 2002). The effect of minocycline on MS was subsequently evaluated in Canada over the last 15 years (Metz et al. 2004, Metz et al. 2017). We have not yet recruited enough patients to confirm the possible effect of minocycline in the treatment of ON.

### 9.10.2 NMOSD

The diagnostic criteria for NMO and the spectrum of NMO diseases have evolved significantly during the last decade. Because of the emerging diversity of the NMO spectrum, the diagnostic criteria will likely continue to develop in the future. While the relationship of AQP4 antibodies in NMOSD is becoming more refined, further research is necessary to discover the true importance and meaning of MOG antibodies in NMOSD patients.

MS medications have developed rapidly in recent years and in the future it may be possible to personalize MS treatment. Since NMOSD is an even more diverse disease than MS, the need for personalized medication is even more important. Computerized examinations may facilitate NMOSD diagnosis already at onset: AQP4 and MOG antibodies in blood, abnormally intense ON findings in OCT, typical changes in spinal cord MRI, and no demyelinating brain MRI findings. Examining these findings routinely at onset would facilitate arriving at the diagnosis of NMOSD sooner, thus allowing prompt initiation of proper treatment. This may improve the prognosis of NMOSD.

Further genetic studies of NMOSD are needed. This study and other genetic studies have discovered only some possible genetic changes in patients with NMOSD. The most recent study revealed that some genetic variants in the MHC region may contribute to the aetiology of NMOSD (Estrada et al. 2018). The prevalence of this disease is very much dependent on ethnicity and race; it is highest among black people (Flanagan et al. 2016) and variations of prevalence have been documented among different Asian ethnic groups living in the same geographical area (Hor et al. 2018). Therefore, in the future some significant changes in genetic profiles of patients with NMOSD may be revealed. Nevertheless, classical genetic-epidemiologic research, such as twin studies, should be performed in NMOSD to demonstrate the role of genetic factors.

It is unclear what drives the immune response against the optic nerve in NMOSD and in MS. Perhaps there is an anatomical basis for preferential immune attack (e.g. vascular structure, blood brain barrier fragility, optic nerve myelin structure) or there may be specific autoantigens displayed on the optic nerve or in its immediate vicinity. New studies will be needed to address these unknowns.

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*Mika Siuko*
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