Journal of the Neurological Sciences 407 (2019) 116396

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Devic's index case: A critical reappraisal – AQP4-IgG-mediated neuromyelitis optica spectrum disorder, or rather MOG encephalomyelitis?

S. Jarius*, B. Wildemann

Molecular Neuroimmunology Group, Department of Neurology, University of Heidelberg, Germany

ARTICLE INFO

Keywords:
Devic's disease
Neuromyelitis optica (NMO)
NMO spectrum disorders (NMOSD)
Myelin oligodendrocyte glycoprotein (MOG)
MOG encephalomyelitis (MOG-EM)
Optic neuritis
Myelitis
History of neurology
History of neuroscience
History of medicine

ABSTRACT

In 1894, Eugène Devic (1858–1930) and his doctoral student Fernand Gault (1873–1936) reported on a patient with optic neuritis (ON) and myelitis and proposed the name "neuro-myélite optique" for this syndrome. Subsequently, Devic became the eponym of neuromyelitis optica (NMO), which was then referred to as "Devic's syndrome", "Devic's disease" or "Morbus Devic". Thereby, the case became a historical index case of NMO. For many decades little attention was paid to NMO, which most authors considered a clinical variant of multiple sclerosis. However, the discovery of pathogenic antibodies to aquaporin-4 at the beginning of the 21st century revived interest in the syndrome, and AQP4-IgG-positive NMO spectrum disorders (NMOSD) are now studied as prototypical autoimmune diseases. More recently, antibodies to full-length myelin oligodendrocyte glycoprotein (MOG) have been detected in patients with ON as well as in patients with myelitis, some of whom exhibit a clinical phenotype very similar to that described by Devic. This raises the question of whether Devic's patient might have suffered from MOG encephalomyelitis rather than classic NMOSD. In this article, we summarise and discuss the available evidence for and against that hypothesis. We also discuss differential diagnoses and the question whether Devic's patient, who worked as a hatter and had initially been admitted for nervous hyperexcitability and tremor, might have suffered from co-existing erethism ('mad hatter disease'), which is caused by chronic occupational exposure to mercury.

1. Introduction

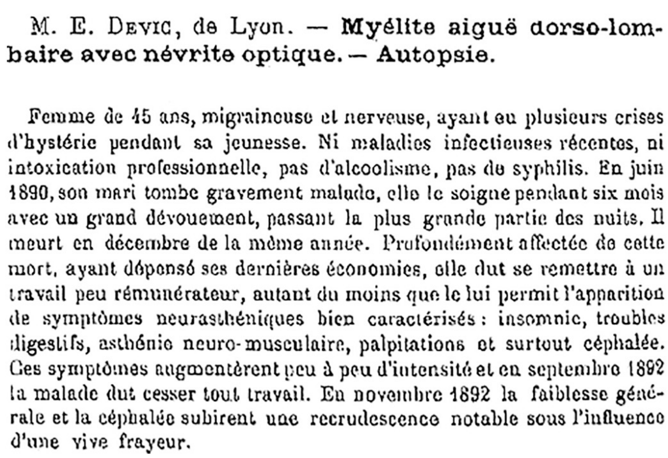
In 1894, Eugène Devic (1858–1930) (Fig. 1) reported on the occasion of the *Congrès Français de Médecine* in Lyon, France, the case of a patient with bilateral optic neuritis (ON) and myelitis and proposed to refer to the syndrome as 'neuro-myélite optique: "*Ces seize cas de myélite aiguë accompagnés de névrite optique sont suffisants pour légitimer la création d'un type clinique, ou plutôt d'un syndrome auquel on pourrait donner le nom de* neuro-myélite optique" [1–3] (Fig. 2). A detailed discussion of that case can be found in the doctoral thesis of Devic's student Fernand Gault (1873–1936), entitled *De la neuro-myélite optique aiguë* [4], which was published later the same year and consisted of a review of the previous medical literature and a clinicopathological analysis of Devic's case (Fig. 3). The novel term was soon adopted by the neurological community [2]. English ('acute optic neuromyelitis') [5,6] and Latin ('neuromyelitis optica' [NMO]) [7] translations can be traced back to 1903 and 1904, respectively [2]. In 1907, Peppo Acchioté (1870–1916) proposed for the first time – in a paper communicated by Joseph Babinski (1857–1932) on the occasion of a session of the *Société de Neurologie de Paris* – to make Devic the eponym of NMO [8–10]. Subsequently, 'Devic's syndrome', 'Devic's disease', '*maladie de Devic*' and '*Morbus Devic*' were for many decades used as synonyms of NMO. This gives Devic's case special significance as a historical index case of NMO (although cases of ON and myelitis had occasionally been published before; see, for example, [11–18]). The discovery of pathogenic autoantibodies to aquaporin-4 (AQP4) (published in 2004 [19–24]) led to a major revision of the nomenclature and diagnostic criteria for NMO in 2015 [25], which now distinguish 'AQP4-IgG-positive' and 'AQP4-IgG-negative NMO spectrum disorders' (NMOSD). In 2011, antibodies to myelin oligodendrocyte glycoprotein (MOG) were described in patients with an NMO phenotype [26] and later shown to be probably pathogenic as well. MOG encephalomyelitis (MOG-EM; also termed MOG antibody-associated disease) differs from both AQP4-IgG-positive NMO and MS with regard to immunopathogenesis and is

Abbreviations: AQP4, aquaporin-4; CNS, central nervous system; CTD, connective tissue disorder; EM, encephalomyelitis; IgG, immunoglobulin G; LETM, longitudinally extensive transverse myelitis; MOG, myelin oligodendrocyte glycoprotein; MS, multiple sclerosis; NMO, neuromyelitis optica; NMOSD, NMO spectrum disorders; ON, optic neuritis

* Corresponding author at: Otto Meyerhof Center, Im Neuenheimer Feld 350, 69120 Heidelberg, Germany;
E-mail addresses: sven.jarius@med.uni-heidelberg.de (S. Jarius), brigitte.wildemann@med.uni-heidelberg.de (B. Wildemann).

https://doi.org/10.1016/j.jns.2019.07.014
Received 15 May 2019; Received in revised form 1 July 2019; Accepted 10 July 2019
Available online 11 July 2019

Fig. 1. Eugène Devic (1858–1930).



M. E. Devic, de Lyon. — **Myélite aiguë dorso-lombaire avec névrite optique. — Autopsie.**

Femme de 45 ans, migraineuse et nerveuse, ayant eu plusieurs crises d'hystérie pendant sa jeunesse. Ni maladies infectieuses récentes, ni intoxication professionnelle, pas d'alcoolisme, pas de syphilis. En juin 1890, son mari tombe gravement malade, elle le soigne pendant six mois avec un grand dévouement, passant la plus grande partie des nuits. Il meurt en décembre de la même année. Profondément affectée de cette mort, ayant dépensé ses dernières économies, elle dut se remettre à un travail peu rémunérateur, autant du moins que le lui permit l'apparition de symptômes neurasthéniques bien caractérisés : insomnie, troubles digestifs, asthénie neuro-musculaire, palpitations et surtout céphalée. Ces symptômes augmentèrent peu à peu d'intensité et en septembre 1892 la malade dut cesser tout travail. En novembre 1892 la faiblesse générale et la céphalée subirent une recrudescence notable sous l'influence d'une vive frayeur.

Fig. 2. Heading and first paragraph of Eugene Devic's famous abstract for the *Congrès Français de Médecine* in Lyon in 1894.

thus now considered a disease entity in its own right by most experts [27–29]. However, a substantial number of patients with MOG-EM meet the current diagnostic criteria for 'seronegative NMOSD' due to significant, albeit incomplete, overlap in the clinicoradiological presentation between the two conditions [25,27,30–34].

Considering that overlap, the question arises of whether Devic's index patient may have suffered from MOG-EM rather than NMOSD. Here, we summarise and discuss the available evidence for and against the hypothesis that the symptoms described by Devic were caused by MOG-EM rather than AQP4-IgG-positive NMOSD and evaluate other possible differential diagnoses as well as possible comorbidities.

We will first give a brief outline of the case. This will be followed by a detailed appraisal of all features related to optic nerve damage (Section 3), spinal cord damage (Section 4) and possible brain involvement (Section 5).

2. Case summary

Devic's patient, a 45-year-old hatter who had recently lost her husband to heart disease, was admitted for suspected "neurasthenia" to the *Hôtel-Dieu de Lyon*. One month after admission she suddenly developed acute complete paraparesis and substantial visual loss. She died another 5 weeks later, most likely from bedsores and/or renal complications. An autopsy was performed, comprising gross macroscopic examination of the inner organs and the brain as well as more detailed macro- and microscopic scrutiny of the optic nerves and the spinal cord.

3. Optic nerve

3.1. Bilateral ON at onset

Both eyes were affected in Devic's patient from the outset. For a long time, bilateral ON was considered a highly typical feature of NMO, a notion that owed much to it being present in Devic and Gault's patient. As a consequence, bilateral ON would later be included as an either obligatory [35] or supportive criterion in, now partly obsolete, definitions of and diagnostic criteria for NMO [25]. However, recent studies have shown that unilateral rather than bilateral ON is the most common initial presentation of NMO [36]. In a large European study, only around 20% of all NMO patients presenting with ON at onset had bilateral ON [36]. However, a marked difference between AQP4-IgG-positive and MOG-IgG-positive patients has been noted. While bilateral involvement was present in only 9/63 (14.3%) at onset in AQP4-IgG-positive patients with ON, both eyes were affected in 41% (15/37) of MOG-IgG-positive ON patients at onset in that study [31]. The fact that Devic's patient presented with bilateral ON at onset is thus more suggestive of MOG-EM than NMOSD. While, as matter of course, it does not prove the diagnosis, it justifies a closer look at the case.

3.2. Marked disc oedema

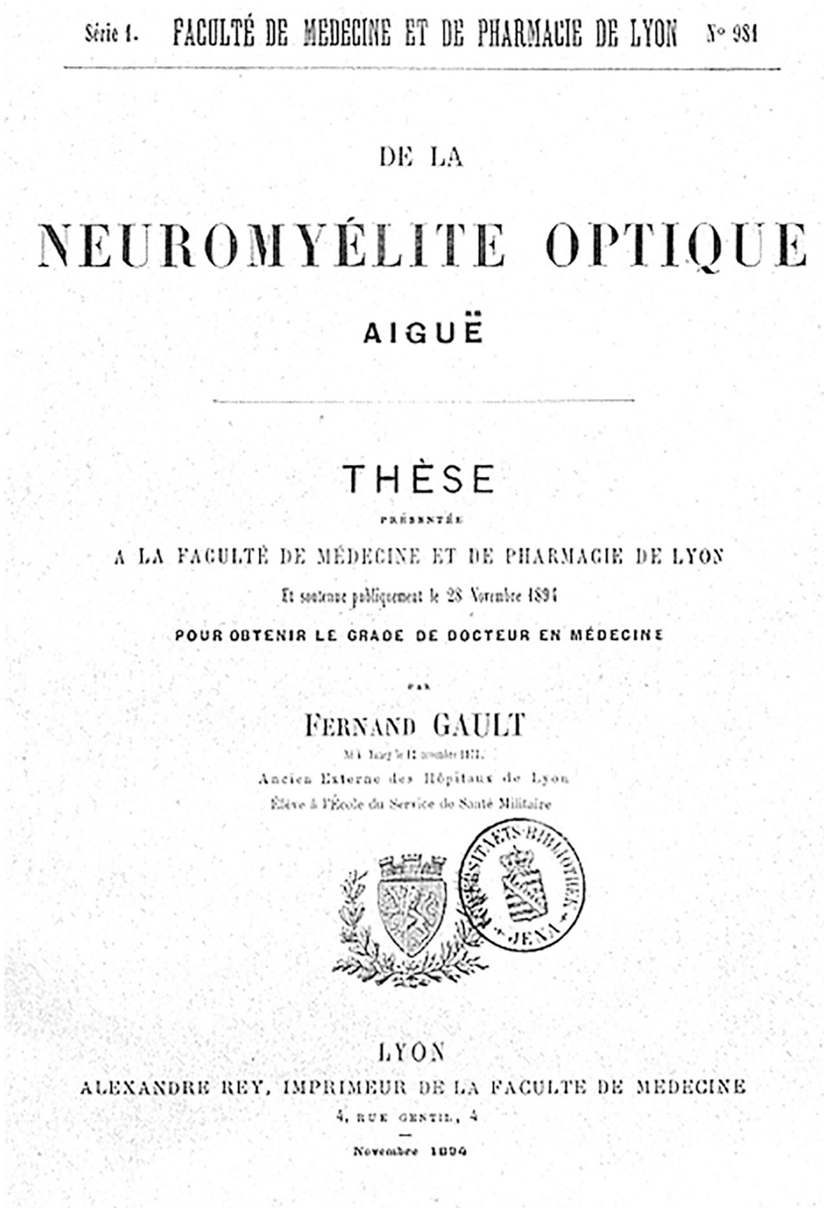
In Devic's congress abstract [3] we are informed that *"l'examen ophtalmoscopique révèle l'existence d'un œdème papillaire très prononcé"*. A more detailed description of the ophthalmoscopical findings can be found on pp. 65 and 73 of Gault's dissertation, where we read:

> *"A l'examen ophtalmoscopique, on trouve un œdème bien marqué de la papille. Les bords sont entièrement flous. La papille est rouge gris. Les vaisseaux paraissent comme enfoui dans la masse. La papille fait une forte saillie. […] L'œdème de la papille est très net".*

As no brain oedema, brain tumour, inflammatory brain lesion (at least none apparent to the naked eye) or brain infarction or bleeding was noted upon autopsy, as explicitly stated by Devic and Gault, papilloedema due to increased intracranial pressure, the most important differential diagnosis of papillitis, can be ruled out with reasonable certainty. This renders anterior ON the most likely cause.

The combination of bilateral ON with marked optic disc oedema (indicating papillitis) is of all findings in support of a diagnosis of MOG-EM the most persuasive one. Disc oedema was present in at least 50% (15/30; no data in another 13 patients) of MOG-IgG-positive patients with a history of ON in a recent European study [31], and at onset even in 86% (36/42) in a North-American cohort [37]. Similarly, optic nerve head swelling was noted in 9/11 children (82%) and 18/19 adults (95%) in an Australian study [38]. By contrast, AQP4-IgG-positive ON affects more frequently the retrobulbar portion of the optic nerve, the optic chiasm and the optic tracts [25,39].

Interestingly, optic neuritis was classified by Devic and Gault as retrobulbar in only *"cinq ou six"* of 17 cases retrospectively evaluated. They concluded *"[d]ans la neuro-myélite aiguë, la papillite est beaucoup plus fréquente que la névrite rétro-bul[b]aire",* and pointed to the fact that there were *"presque jamais de douleurs par les mouvements de l'œil"* [4]. This is in apparent contrast to what we know about AQP4-IgG-positive NMO.


Série 1. FACULTÉ DE MEDECINE ET DE PHARMACIE DE LYON N° 981

DE LA

NEUROMYÉLITE OPTIQUE

AIGUË

THÈSE

PRÉSENTÉE

A LA FACULTÉ DE MÉDECINE ET DE PHARMACIE DE LYON

Et soutenue publiquement le 28 Novembre 1894

POUR OBTENIR LE GRADE DE DOCTEUR EN MÉDECINE

PAR

FERNAND GAULT

Ancien Externe des Hôpitaux de Lyon

Élève à l'École du Service de Santé Militaire

LYON

ALEXANDRE REY, IMPRIMEUR DE LA FACULTE DE MEDECINE

4, RUE GENTIL, 4

Novembre 1894

Fig. 3. Title page of Fernand Gault's doctoral thesis "De la neuromyélite optique aiguë" (Lyon, November 1894).

3.3. Demyelination of the optic nerve

While CNS lesions in MOG-IgG-positive patients are primarily characterised by plaque-like demyelination with relative axonal preservation, severe astroglial damage and secondary demyelination, as well as axonal loss, are typically present in AQP4-IgG-positive NMOSD [40–44]. It may thus be taken as evidence for MOG-EM that Devic and Gault seem to have mentioned loss only of myelin sheaths, not of glial cells or axons, in describing their patient's optic nerve lesions:

> *"On note une disparition presque complète des tubes à myéline. Dans presque tous ceux qui possèdent encore un peu de leur gaine de myéline, celle-ci est discontinue et nettement fragmentée".*

An exclusively demyelinating lesion would indeed support a diagnosis of MOG-EM and argue against a diagnosis of AQP4-IgG-positive NMOSD.

However, there are two limitations: First, and most importantly, the accompanying spinal cord lesions are described as being not only demyelinating in nature but also highly destructive, as will be outlined in more detail below (see Section 4.3). As long as we do not suppose two different pathogeneses for the optic nerve lesion on the one hand and the spinal cord lesion, which occurred almost simultaneously, on the other hand, the description of the spinal lesions strongly argues against MOG-EM. Second, a potential, though minor, limitation is that it is not completely clear whether by the term *"tubes à myeline"* Devic and Gault referred to the myelin sheaths only, or rather to the myelinated nerve as a whole. The distinction between myelin sheaths and axons was already well established in the 1890s: osmium staining had been invented in 1865, and Charcot and his school already explicitly distinguished the axon as part of the nervous tube in 1868 when describing typical MS lesions: *"Le tube nerveux n'est donc plus représenté, à la fin, que par le cylindre d'axe"* [45]. By contrast, nowhere in Devic's or Gault's reports on this patient is the term axon (or *cylindre d'axe*) used; thus, axons and myelin sheaths are nowhere explicitly distinguished from one another.

3.4. Severe visual loss

At first glance, Gault's report might suggest an only relatively moderate degree of visual loss, which could be mistaken as a further argument in favour of MOG-EM:

> *"[L]a malade ne pouvait plus distinguer une pièce de 5 francs d'une pièce de 20 centimes quand on plaçait ces pièces de monnaie à plus de 10 centimètres de ses yeux […] La malade ne distingue plus une épingle placée devant ses yeux."*

However, elsewhere we are informed that the light reaction vanished almost completely later in the disease course, with the pupils "[*restantes] égales et dilatées*". Accordingly, Devic, in his congress abstract, describes the visual loss as "*considérablement*".

While some studies suggested that MOG-EM takes a milder course than AQP4-positive NMOSD, more recent studies have anyway demonstrated that a substantial proportion of patients with MOG-ON develop severe ON as well. In a European cohort, attack-related functional blindness (defined as visual acuity [VA] ≤ 0.1) in one or both eyes occurred at least once in 27/39 patients (69.2%) and VA ≤ 0.5 was present at least once in 33/39 patients (84.6%) during acute ON attacks [46]. Moreover, mild ON attacks may occur also in AQP4-NMOSD. The degree of visual loss is therefore not a suitable discriminator.

3.5. Retinal haemorrhages

A highly interesting and surprising finding in Devic's patient is that of retinal haemorrhages. In Devic's congress abstract we read:

> *"La marche de l'affection prend, à partir de ce moment, une allure encore plus aiguë, le 8 février [i.e. one week after disc oedema was first noted] on constate la présence d'hémorrhagies rétiniennes multiples. […] [Environ deux semaines plus tard] les hémorrhagies rétiniennes sont stationnaires".*

And Gault further specifies in his dissertation: *"A l'examen ophtalmoscopique*: *hémorragies rétiniennes au côté gauche, à la partie inférieure et externe de la papille, point sur l'œil droit […] constate la présence d'hémorrhagies rétiniennes multiples".*

Summarising what he learned from his case and from his review of the literature, he concluded:

> *"Les hémorragies ne sont pas rares et se présentent sous forme de foyers d'extravasations sanguines. On remarque aussi des exsudats plus ou moins abondants qui, empiétant sur les bords de la papille, contribuent encore à rendre ses limites moins distinctes."*

Despite that fact, little attention was paid to retinal haemorrhages in NMOSD and MOG-EM until very recently. In 2017, Biotti et al. reported retinal haemorrhages in 6/47 French MOG-IgG-positive patients with ON (pericapillary in four cases, punctuate perimacular in two) [47]. Retinal haemorrhages in association with disc oedema were recently also noted in North-American patients with MOG-ON [37]. Finally, two case reports have been published on MOG-IgG-positive patients with optic disc oedema, retinal haemorrhages and a macular star (as usually seen in neuroretinitis) [48,49]. By contrast, retinal haemorrhages have, to the best of our knowledge, not been described in patients with AQP4-IgG-positive ON (except in patients suffering from opportunistic infections of the retina under immunosuppressive treatment [50]). Although systematic studies on the topic are lacking, it seems somewhat unlikely that an association of AQP4-positive NMOSD with retinal haemorrhages has been overlooked in the past, given that patients presenting with AQP4-IgG-positive ON – at least at all major centres – routinely undergo fundoscopy and given the large number of studies on optical coherence tomography findings in NMOSD [33,51–54]. The presence of retinal haemorrhages in Devic's patient thus supports a diagnosis of MOG-EM rather than AQP4-IgG-positive NMOSD.

As a limitation, however, retinal haemorrhages also occur in other inflammatory conditions, including a number of autoimmune disorders:

(a) Patients with paraneoplastic autoimmunity to CV2/CRMP may present with an NMO-like phenotype with bilateral papillitis and retinal haemorrhages [55–57]. While no tumour was found upon gross autopsy examination in Devic's patient, it should be kept in mind that tumours underlying paraneoplastic neurological disorders can still be minute (sometimes only detectable microscopically or within lymph nodes) at the time of onset of the neurological syndrome. Signs and symptoms compatible with a tumour in Devic's patient include significant weight loss, digestive problems and obstipation, all of which preceded the onset of ON and myelitis.
(b) Connective tissue disorders (CTD) such as systemic lupus erythematosus and vasculitis may also cause ON with retinal haemorrhages. Of note, AQP4-IgG-positive NMOSD (but not MOG-IgG) is often associated with other autoimmune diseases [30,31,58–62], including CTD. While no other clinical signs or symptoms indicative of a CTD were given by Devic and Gault, there is still the possibility that NMO emerged as the first manifestation of such a disorder: several reports on ON and/or transverse myelitis as the initial clinical manifestation of CTD have been published, including in AQP4-IgG- and MOG-IgG-negative patients (*e.g.*, [63,64]).
(c) Further conditions reported to cause retinal haemorrhages include Behçet disease [65], sarcoidosis, lymphoma, increased intracranial pressure, anterior ischaemic optic neuropathy, and viral (CMV, HSV), parasitic and fungal infections. However, no signs of recent infection (including tuberculosis) were noted at admission, and no microbiological examinations were performed, neither pre- nor post-mortem. Of note, Gault considered an infectious aetiology of NMO nevertheless conceivable, as he states in the very last paragraph of his dissertation:

> *"Ce syndrome relève probablement dans un certain nombre de cas de l'infection. C'est un exemple nouveau d'un processus infectieux, frappant à la fois deux points éloignés du système nerveux sans qu'il y ait de lésions anatomiques quelconques reliant ces deux foyers."*

3.6. Summary

Bilateral visual loss, bilateral optic oedema and retinal haemorrhages at disease onset are all more suggestive of MOG-EM than of AQP4-IgG-positive NMO, particularly in combination; however, a number of differential diagnoses need to be considered. The degree of visual loss is compatible with both disorders. The histopathological information provided needs to be interpreted with caution and in the light of the more detailed information given on the histopathology of the spinal cord lesions.

4. Spinal cord

4.1. Predominant involvement of the lower spinal cord

On the day the bilateral disc oedema and visual loss were first noted, Devic's patient also developed paresis of the entire right leg with no significant loss in sensitivity and with preserved tendon reflexes. Moreover, marked urinary retention was recognised, which required regular catheterisation. Five days later, paresis of the left leg occurred and areflexia was noted on both sides. On day 8, sensorimotor paraplegia was complete. The upper extremities and the face showed no trace of paresis or sensory disturbances.

At autopsy, *"une diminution de consistance au niveau du renflement dorso-lombaire* "was noted as well as *"une coloration jaune grisâtre qu'on ne rencontre pas sur d'autres points"*. The authors concluded that *"la paraplégie relevant d'une altération du renflement lombaire"*.

Abnormalities in spinal cord MRI have been reported to be more frequently present in the cervical and upper thoracic spinal cord segments than in the lower thoracic and lumbar regions in AQP4-IgG-positive myelitis [25,66,67]; by contrast, a tendency has been reported for MOG-EM to more frequently affect the lower regions of the spinal cord

[66]. The predominant involvement of the lumbar enlargement would thus rather support a diagnosis of MOG-EM than NMOSD in Devic's patient. However, the intramedullary location of the lesion, its extension and its histological features need to be taken into account, too.

4.2. Lack of LETM?

Longitudinally extensive transverse myelitis (LETM), as defined by the presence of a contagious spinal cord lesion extending over three or more vertebral segments, is a typical feature of AQP4-IgG-positive NMOSD (present during at least one attack in 93% of patients presenting with myelitis at onset [36]). It is less frequent in patients with MOG-EM (in 65% of patients with myelitis at onset in [46]). Although spinal cord lesions affecting less than three vertebral segments occasionally occur in patients with AQP4-IgG-positive myelitis (depending partly on the timing of MRI), the absence of LETM would render a diagnosis of AQP4-IgG-related NMOSD in Devic's patient less likely and could thus be put forward as an additional argument in support of MOG-EM. Gault's description on page 68 of his dissertation of the lumbar lesion spanning over *"4 ou 5 centimètres, au maximum"* at the time of autopsy seems in fact to argue against the presence of LETM.

However, elsewhere (p. 71) we read:

> *"Les lésions que nous venons d'énumérer persistent avec le même caractère dans la moelle dorsale inférieure, mais atténuées de plus en plus. Cependant on les retrouve encore avec une assez grande netteté à 3 centimètres au-dessus du renflement dorso-lombaire."*

As neither Devic nor Gault mentions the presence of more than one spinal cord lesion, it seems from that statement that the lesion in the lumbar enlargement extended around 3 cm into the adjacent lower dorsal segments of the spinal cord. In that case, LETM would be more likely (based on normal values for vertebral body and intervertebral disc heights in adults). Moreover, on p. 70, Gault mentions severe damage not only of Goll's tract (gracile fasciculus) but also of Burdach's tract (cuneate fasciculus), which usually begins to enter the spinal cord only at level T6, suggesting that the lesion extended far beyond the lumbar enlargement. Finally, urinary retention, bowel incontinence and reduced or absent lower extremity reflexes, as present in Devic's patients, would be compatible with involvement also of the adjacent conus segments. In summary, this gives the impression of a rather large, longitudinally extensive spinal cord lesion which would be compatible both with MOG-EM and with AQP4-IgG-positive NMOSD. As a limitation, it should be kept in mind that not only NMOSD and MOG-EM but also a number of other conditions can cause LETM, with or without concomitant optic neuritis, including, for example, sarcoidosis [68–70].

4.3. High degree of tissue destruction in the spinal cord

Gault's description of the spinal cord lesions on p. 70 of his dissertation suggests severe tissue damage:

> *"Dans la partie du cordon postérieur qui ne prend plus l'hématoxyline, on ne trouve guère qu'un réseau névroglique, dense, épais et rempli des éléments cellulaires."*

Accordingly, the lesions are described by Devic in his congress abstract as "*inflammatoires et destructives*".

This argues against a diagnosis of MOG-EM, in which tissue damage is thought to be usually restricted to damage to the myelin sheaths with no major loss in neuronal and glial cell numbers [44, 71]. The fact that only the glial scaffold remained is reminiscent more of spinal infarction than of MOG-EM.

However, the fact that the spinal histopathological findings tend not to support a diagnosis of MOG-EM does not prove that the patient had AQP4-IgG-positive NMOSD: Devic's above-mentioned description of the glial scaffold being the only structure left within the spinal cord lesion not only argues against MOG-EM but is also not directly suggestive of AQP4-IgG-positive NMOSD. While astrocytes are preserved in MOG-EM, they are the primary target in AQP4-IgG-positive NMOSD and are destroyed early in the process of lesion formation.

As a potential limitation, we cannot know with absolute certainty whether the marked *"réseau fibrillaire"*, which Devic described as consisting of *"fibrilles sont en grande quantité"* and to be stained "*rosé*" by Ranvier's picro-carmine (while there was at the time no staining method selective for neuroglia, carmine would – in contrast to Weigart's method – stain neuroglial structures in addition to neuronal axons, but not myelin; see, for example, Joseph Jules Dejerine's [1849–1917] chapter on staining methods in his *Anatomie des Centres Nerveux* [1895] [72]), really represented the glial remnants of a severely inflammatory and destructive process or was the result of reactive gliosis. However, given that the "fibrillary network" still contained white blood cells and considering the relatively young age of the lesion, which was probably still active at the time the patient died (her symptoms worsened the day before death), the former hypothesis seems at least more likely.

Most other histological features reported by Devic and Gault do not favour a diagnosis of MOG-EM but are equally compatible with both MOG-EM and AQP4-IgG-positive NMOSD. These include the presence of blood-borne inflammatory cells both in the perivascular spaces and, to a lesser extent, in the more remote tissue; involvement of both the white and the grey matter; presence of large, osmic acid-positive cells probably corresponding to myelin-loaded macrophages; absence of haemorrhagic foci; and lack of peripheral nerve demyelination. None of these findings seems apt to specifically support either of the two diagnoses.

It might be irritating to some readers that a loss of oligodendrocytes is not explicitly mentioned by Devic and Gault. This could be mistaken as an argument in favour of MOG-EM and against AQP4-IgG-positive NMOSD: Oligodendrocytes are typically lost in AQP4-IgG-positive NMO but are relatively preserved in MOG-EM [44], which is characterised mainly by a loss of myelin sheaths. However, such an argument would clearly be invalid, as it overlooks the fact that oligodendrocytes – Cajal's mysterious 'third element' – were still unknown and the respective staining methods not yet established when Devic and Gault's reports appeared in 1894. William Ford Robertson (1867–1923) would publish his observations only around 5 years later [73,74], and Pío del Río-Hortega's (1882–1945) two ground-breaking studies, in the latter of which he coined the term 'oligodendrocyte', would appear only in 1919 and 1921 [75,76] (see [77] for a recent review on the topic).

4.4. Thickened vessel walls with inflammatory infiltrates

Thickening of the vessel walls, mentioned by Gault on p. 69 of his dissertation, is compatible with AQP4-IgG-positive NMOSD, but has not been mentioned in any of the histopathological studies on MOG-EM published so far and also not in any of the unpublished cases we are aware of. While no thrombosis was noted in the lesions examined, *"la lumière de plusieurs de ces vaisseaux est rétrécie de ce fait"*. Narrowing of the vessel lumina was also noted in the optic nerve: *"Les artères sont rétrécies, filiformes"*.

More strikingly, Devic and Gault describe inflammatory cell infiltrates within the vessel walls (*"Et, sur plusieurs points, l'on peut voir de jeunes éléments cellulaires infiltrant ces parois vasculaires"*), a feature suggestive of vasculitis but rather not of AQP4-IgG-positive NMOSD or MOG-EM (in two recently published cases of MOG-EM in which small-vessel vasculitis was initially suspected [104], re-evaluation of the paraffin blocks did not confirm that diagnosis; in both cases, the vessel walls were not affected [105]). Vasculitis may occur as an isolated phenomenon or associated with CTD, a common accompaniment of AQP4-IgG-positive NMOSD. However, vasculitis may also arise as a complication of infectious diseases such as syphilis and neuroborreliosis.

4.5. Predominant involvement of the dorsal columns

From the autopsy report it seems that the spinal cord white matter lesion involved mainly the gracile fasciculus (Goll's tract) and the cuneate fasciculus (Burdach's tract). In both fasciculi, *"tubes colorés par l'hématoxyline"* (*i.e.* myelinated fibres) were almost completely absent. In the latter tract only the above-mentioned glial scaffold was left. As another sign of severe inflammation, the two edges of the posterior fissure, which normally separates the left and the right dorsal column, appeared 'welded' together. In the upper part of the dorsal as well as in the cervical spinal cord, marked sclerosis of Goll's tract was noted. By contrast, only mild sclerotic damage was found in the remaining white matter except for minor sclerotic and degenerative changes of the pyramidal tract:

> *"Quant aux autres portions de la substance blanche, les lésions sont peu marquées et on ne trouve à signaler qu'une zone de sclérose légère tout à fait corticale et située spécialement dans la région du cordon latéral […] A la partie inférieure de la moelle lombaire, on ne retrouve guère que la dégénérescence du faisceau pyramidal, surtout du faisceau pyramidal croisé".*

It is difficult to interpret these findings: Both AQP4-IgG-positive NMOSD and MOG-EM may indeed cause damage to the spinal cord white matter (though the former affects predominantly the central portion of the spinal cord [25,78]). However, predominant involvement of the dorsal columns has so far not been recognised as a characteristic feature of either of the two conditions. By contrast, it is a typical feature of several other – autoimmune as well as metabolic and infectious – conditions:

(a) Demyelination of the dorsal columns is a typical finding in tabes dorsalis, a highly common disease at Devic's time, which can also lead to optic nerve atrophy. However, given the severe inflammatory nature of the patient's lesion, the marked paresis, the rapid course and the lack of other typical symptoms such as lancinating pain, classic tabes seems highly unlikely. As a limitation, it should not go unmentioned that the protean manifestations of neurosyphilis are thought by some authors also to include rare instances of syphilitic acute optic neuritis/papillitis and myelitis [79,80]. According to Gault's report, no signs suggestive of recent or chronic syphilis were present in their patient. *Treponema pallidum* was unknown at the time Devic and Gault's reports appeared, and tests would only become available more than a decade later.

(b) Damage to the posterior columns is also characteristic for subacute combined degeneration of the spinal cord (SCDSC), a condition caused by vitamin B12 deficiency. SCDSC can be associated with optic neuropathy. Interestingly, vitamin B12 deficiency has been reported in association with AQP4-IgG-positive NMOSD [81]. As AQP4-IgG does not only bind to astrocytic AQP4 but also to AQP4 expressed at the basal membrane of intrinsic factor-producing parietal cells in the stomach, SCDSC might hypothetically occur as a complication of AQP4-IgG-positive NMOSD in some cases. While severe inflammatory infiltration would be atypical for SCDSC, its occurrence in the context of an autoimmune disease affecting the spinal cord, such as AQP4-IgG-positive NMOSD or MOG-EM, might change the overall histopathological picture substantially. This said, the fact that the glial network, the primary target in NMOSD, was the only structure apparently left in the lesion studied by Devic argues against AQP4-IgG-positive NMOSD, as discussed above, and thus also against a combination of SCDSC with AQP4-IgG-mediated autoimmunity.

(c) Predominant involvement of the dorsal columns has been reported in patients with "LHON plus", *i.e.*, in patients with Leber's hereditary optic neuropathy (LHON) who develop additional brain and/or spinal cord lesions [82]. LHON plus may present as a hyperaemic, "pseudo-oedematous" elevated optic nerve with peripapillary telangiectasias. Histopathologically, LHON plus is characterised by destructive and demyelinating white-matter changes with axonal damage [83]. Interestingly, two reports on NMO patients with both anti-AQP4 antibodies and a LHON-associated pathogenic mitochondrial DNA mutation have recently been published [84,85].

Finally, the predominant affection of the dorsal column could simply have been by chance. In accordance with the nearly ubiquitous expression of AQP4 and MOG in the CNS, lesion location varies considerably in both AQP4-IgG-positive NMOSD and in MOG-EM, despite the identification of predilection sites.

4.6. Areflexia

MS patients typically present with hyperreflexia and spastic paresis, and both symptoms are also commonly seen in AQP4-IgG-positive NMOSD and MOG-EM. The fact that Devic's patient presented with areflexia (*"les réflexes tendineux qui avaient été jusqu'ici trouvés normaux ou seulement un peu diminués, furent complètement abolis")* may thus seem unusual and suggest additional damage to the spinal roots or peripheral nerve. However, in patients with severe damage to the lower parts of the spinal cord (e.g. in conus syndrome) and following damage to the anterior horn cells, hypo- and areflexia are not, in fact, rare phenomena. In Devic's case, both qualitative alterations of the anterior horn cells (*"on en trouve cependant peu avec leurs prolongements"*) and anterior horn cell loss (*"on constate un assez grand nombre d'amas arrondis, sans prolongements qui sont probablement les vestiges de cellules altérées"*) were noted. In patients presenting with acute paresis and areflexia, the combination of the latter with mass movements and exaggerated cutaneous reflexes – as present in Devic's patient ("*Les réflexes cutanés, contrairement aux réflexes tendineux, persistent et allèrent même en augmentant, à tel point que quelques jours avant la mort il suffisait d'exciter légèrement la plante d'un pied pour amener une contraction réflexe d'un grand nombre de muscles des deux membres inférieurs")* – is highly indicative of a spinal origin of the paresis. Of note, several reports on areflexia in patients with LETM have appeared in recent years, some of whom were MOG-IgG-positive or, less frequently, AQP4-IgG-positive [66,86,87]. The presence of areflexia thus does not argue against a diagnosis of MOG-EM or AQP4-IgG-positive NMOSD in Devic's patient.

As a limitation, areflexia may also occur in cases of infectious or postinfectious transverse myelitis as well as in patients with transverse myelitis and accompanying spinal acute inflammatory demyelinating polyradiculoneuropathy. At least macroscopically, however, the spinal roots arising from the lumbar enlargement were not altered in Devic's patient and there was no sign of infection preceding the onset of symptoms.

4.7. Summary

The predominant involvement of the lumbar spinal cord tends to support MOG-EM more than AQP4-IgG-positive NMOSD. LETM is likely and would be compatible with both disorders, while a short lesion would not be supportive of a diagnosis of AQP4-IgG-positive NMOSD. On the other hand, the histopathological findings argue against MOG-EM but are also not suggestive of AQP4-IgG-positive NMOSD. The preferential involvement of the dorsal columns is not typical for either of the two conditions, but also does not preclude them, and is compatible with a number of other diagnoses as well. Areflexia is not a typical feature but consistent with possible conus involvement. Considering the vascular changes (vessel wall infiltration; thickening of the vessel walls; narrowed vessel lumen) and the stroke-like appearance of the lesions (preservation of only the glial scaffold), isolated, CTD-associated or (post)infectious vasculitis needs to be considered as a differential diagnosis.

5. Prodromal symptoms

5.1. Presentation

Upon the patient's admission, Devic made an initial diagnosis of „neurasthenia“, which was later changed to “pseudo-neurasthenia” when urinary retention, papillitis and subsequently myelitis manifested around 4 weeks after admission, proving the presence of an organic disease. During that initial period, the patient had complained of general weakness, beginning several months previously, and had shown signs of depression.

In addition to fatigue and depression, a number of further symptoms compatible with brain or brainstem involvement were noted. These included hyperexcitability, irritability, anxiety and tremor (*“La malade est constamment soucieuse […]. Le moindre bruit, l'évènement le plus insignifiant provoque de la frayeur et une véritable angoisse avec tachycardie et tachypnée. Léger tremblement des mains constitué par de petites oscillations brèves et rapides et s'exagérant beaucoup par l'influence de l'excitation psychique la plus insignifiante”*), severe attacks of paroxysmal hemicrania-like, occipital and ocular headache (*“Actuellement cette insomnie paraît due surtout aux douleurs qu'elle éprouve. Ces douleurs surviennent par accès, tantôt le jour, tantôt la nuit. Elles durent plus ou moins, occupent une moitié de la face et du crâne, quelquefois la moitié gauche, le plus souvent la moitié droite, mais toujours le maximum en est au niveau de la région occipitale, à la nuque et sur les globes oculaires. Ces douleurs sont parfois assez vives pour arracher des cris à la patiente”*), and marked weakness of accommodation.

5.2. Functional “neurasthenia”?

While some of these symptoms are not typical prodromal signs of AQP4-IgG-positive NMOSD or MOG-EM, they may occasionally occur in these conditions: Encephalopathy, which may include psychiatric symptoms, has been described as a rare presentation of NMOSD at onset, though more often in children than in adults [88–91]. Irritability, tremor, insomnia and tachycardia are also typical manifestations of hyperthyroidism. AQP4-IgG-positive NMOSD is often associated with other autoimmune disorders, including autoimmune thyroiditis. Moreover, lesions to the diencephalon, a site of high regional AQP4 expression, are not rare in AQP4-IgG-positive NMOSD. Accordingly, both hyperthyroidism and hypothyroidism have been observed in patients with AQP4-IgG-positive NMOSD. Psychiatric symptoms are also common in patients with CTD, which – as mentioned above – frequently co-exist with AQP4-IgG-positive NMOSD [36,92,93]. It is of note in this context that autopsy revealed vessel wall infiltration in Devic's patient, a finding compatible with CTD-associated vasculitis.

Fatigue was shown to develop over the course of disease in around 70% of AQP4-IgG-positive patients [94] and has also been described in patients with MOG-EM [95,96]. However, it can also not be excluded that the patient's general weakness (*“faiblesse générale”*) leading to admission was the result of previous, minor attacks of myelitis that went unrecognised (the patient had experienced back pain [*“rachialgie”*] months before admission), or reflected a protracted onset of myelitis caused by minor yet smouldering inflammation of the spinal cord. Finally, targeting of sarcolemmal AQP4 by complement-activating IgG occasionally causes myopathy and muscular weakness in patients with NMOSD [97].

In consequence, the prodromal “neurasthenic” symptoms described by Devic do not *per se* argue against a diagnosis of AQP4-IgG-positive NMOSD or MOG-EM. The same holds true for the long duration of the “prodromal” phase. As soon as ON and myelitis had manifested, *“[l]a progression des troubles sensitifs et moteurs [était] rapide”*.

Alternatively, given the lack of supporting evidence for autoimmune thyroiditis (*“[p]as de goitre, pas d'exophtalmie”*), the absence of brain or brainstem lesions detected at autopsy (though only a gross examination was performed) and the lack of myopathic pain as reported in AQP4-IgG-related myopathy, it is also conceivable that some of the “neurasthenic” symptoms were simply functional or resulted from reactive depression unrelated to the neurological disease but rather caused by the death of her husband, whom she had nursed day and night for several months, and from a period of insomnia caused by severe paroxysmal headache that had lasted for at least the past 2 months.

5.3. Co-existing erethism?

It is of interest in this context that the patient worked as a hatter. Some of the symptoms described by Devic – tremor, irritability, hyperexcitability, insomnia (*“presque absolue”*), fatigue, “neurasthenia”, emotional disturbances, depression – would fit well with (but, of course, not prove) a diagnosis of erethism (also termed ‘mad hatter disease’). Although Gault explicitly mentioned that she denied exposure to mercury vapours, some doubt remains: Mercury was a well-established and widely used method to stabilise wool during felting in 19th century in France (for long time treated as a French trade secret), and a law to protect workers from mercury exposure was enacted in France only in 1898. In 1878, at least 159/570 (27%) workers showed the “mercurial disease” in a North-American survey [98]. According to the author of that survey, the true figure may have been even higher, since symptoms and exposure were frequently denied by workers for fear of being dismissed *(“very few indeed would admit that the disease was contracted in their present places”*) [98,99]. Finally, it is unclear whether Gault took into account only recent exposure or also previous, chronic exposure. It is therefore at least conceivable that some of the supposedly prodromal symptoms in Devic's patient were signs of erethism.

It is much less likely that mercury exposure contributed to visual loss and myelitis. Mercury has been shown to be detectable in the spinal cord following inhalation in primates [100], and mercury intoxication has been putatively linked to chronic, degenerative anterior horn cell degeneration (a loss in anterior horn processes as well as a loss in absolute numbers of anterior horn cells was in fact observed in Devic's patient). To the best of our knowledge, however, it has not been linked with acute inflammatory spinal cord damage. Interestingly, though, a clinical and pathological study on victims of the large methylmercury poisoning outbreak in Iraq in 1971–1972 reported visual dysfunction in > 50% of cases, which was associated with papillitis in 13/66 persons, bilateral partial or total blindness in 13/66, and paresis in 42/66 (with paralysis seen only in the severely intoxicated subgroup) [101,102]. Neuropathological changes were allegedly similar to those described during the outbreaks of Minamata disease and included *“complete loss of neurones with hyperplasia of the astrocytes”* [101]. Severe visual loss associated with optic disc swelling between 1.5 and 2 diopters was also reported in 10 patients in [103]. As usual in mercury intoxication, symptoms were first noted some time (10–30 days) after exposure. While it is highly unlikely that Devic's patient was exposed to comparable doses of mercury, it is tantalising to speculate that erethism due to chronic occupational mercury intoxication may have been present in addition to a primarily inflammatory acute disorder, explaining some of the peculiar prodromal symptoms described by Devic and Gault.

5.4. Summary

The relatively long period of psychiatric and psychological symptoms that preceded the onset of ON and myelitis in Devic's patient is typical neither for MOG-EM or AQP4-IgG-positive NMOSD, especially in the absence of brain and brainstem lesions, but *per se* does not rule out these conditions either. However, a simple coincidence cannot be excluded.

6. Disease outcome

Finally, it may appear that the fatal outcome argues in favour of

AQP4-IgG-positive NMOSD and against MOG-EM, which is believed to follow a milder course. However, Devic's patient probably died either from sepsis caused by the severe, ulcerated sacral bedsores that she contracted 10 days after the paresis had started (a very common cause of death from myelitis until well into the 20th century) or from renal failure or urinary sepsis (*"l'urine est ammonicale"*, *"fever"*) caused by severe urinary retention, conditions which can complicate not only AQP4-IgG-positive NMOSD but also MOG-EM. Moreover, rare fatal cases of MOG-IgG-EM have been reported in the meanwhile, contradicting the stance that MOG-EM generally takes a mild course [31].

7. Conclusion

In summary, we believe that there is insufficient evidence to support the hypothesis that Devic's index patient had MOG-EM rather than AQP4-IgG-mediated NMOSD. While some of the clinical findings are indeed suggestive of MOG-EM (bilateral ON; marked disk oedema; involvement mainly of the lumbar spinal cord), other features do not suggest MOG-EM or are – based on what we know about MOG-EM to date – at least atypical (severe tissue damage leaving only the glial network intact; vessel wall infiltration; thickened vessel walls with marked narrowing of the vessel lumina; demyelination mainly of the dorsal columns). Moreover, some features cannot be fully evaluated due to lacking or imprecise data and others are compatible with both AQP4-IgG-positive NMOSD and MOG-EM. Finally, a diagnosis other than AQP4-IgG-positive NMO and MOG-EM cannot be completely excluded, given that some of the histopathological findings reported by Devic and Gault are not strongly suggestive of AQP4-IgG-positive NMOSD either. The differential diagnoses that have to be considered include, among others, postinfectious encephalomyelitis, connective tissue disorders, and vasculitis. We conclude that the precise diagnosis in Devic's index patient remains elusive.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available but are available from the corresponding author upon reasonable request.

Declaration of Competing Interests

B.W. reports grants from the German Ministry of Education and Research, grants from the Dietmar Hopp Foundation, grants from the Klaus Tschira Foundation, personal fees from Bayer Healthcare, personal fees from Biogen, grants and personal fees from Merck Serono, grants and personal fees from Novartis, grants and personal fees from Sanofi Genzyme and grants and personal fees from TEVA, none of which were related to the submitted work.

S.J. reports no competing interests.

Funding

The work of B.W. was supported by research grants from the Dietmar Hopp Foundation, Merck Serono and the German Federal Ministry of Education and Research (BMBF/KKNMS, Competence Network Multiple Sclerosis).

Authors' contributions

S.J. conceived and designed the study, collected the data, analysed the data and wrote the manuscript. Both authors were involved in revising the manuscript for intellectual content. Both authors read and approved the final draft before submission.

Acknowledgements

We would like to thank the Dietmar Hopp Foundation, Merck Serono and the German Federal Ministry of Education and Research-funded Competence Network Multiple Sclerosis (KKNMS) for funding work on the differential diagnosis of MS.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2019.07.014.

References

[1] E. Devic, Myélite subaiguë compliquée de névrite optique, Bull. Méd. 8 (1894) 1033–1034.
[2] S. Jarius, B. Wildemann, The history of neuromyelitis optica, J. Neuroinflammation 10 (2013) 8.
[3] E. Devic, Myélite aiguë dorso-lombaire avec névrite optique - Autopsie, Congrès français de médecine (Premiere Session; Lyon, 1894; Procès-verbaux, mémoires et discussions; Publiés par M le Dr L Bard), Asselin et Houzeau, Louis Savy, Lyon, 1895, pp. 434–439.
[4] F. Gault, De la neuromyélite optique aiguë. Thèse. Faculté de Médecine et de Pharmacie, Lyon, Alexandre Rey, 1894.
[5] Anonymous, Acute optic neuromyelitis, Ophthlamoscope 1 (1903) 230–231.
[6] Anonymous, Acute optic neuromyelitis, Br. Med. J. 2 (1903) 37–38.
[7] E. Stransky, 22 Neuromyèlite optique aiguë, par E. Brissaud et Brécy. (Review neurologique. 1904. Nr. 2), Neurologisches Centralblatt 23 (1904) 823–824.
[8] P. Acchiote, Sur un cas de neuromyélite subaiguë ou maladie de Devic, Bulletin officiels de la Société de neurologie de Paris 8-9 (1907) 273–275.
[9] P. Acchiote, Sur un cas de neuromyélite subaiguë ou maladie de Devic, Annales d'oculistique 70th year (1907) 374.
[10] P. Acchiote, Sur un cas de neuromyélite subaiguë ou maladie de Devic, Rev. Neurol. 15 (1907) 775–777.
[11] S. Jarius, B. Wildemann, The case of the Marquis de Causan (1804): an early account of visual loss associated with spinal cord inflammation, J. Neurol. 259 (2012) 1354–1357.
[12] S. Jarius, B. Wildemann, 'Noteomielite' accompanied by acute amaurosis (1844). An early case of neuromyelitis optica, J. Neurol. Sci. 313 (2012) 182–184.
[13] S. Jarius, B. Wildemann, On the contribution of Thomas Clifford Allbutt, F.R.S., to the early history of neuromyelitis optica, J. Neurol. 260 (2013) 100–104.
[14] S. Jarius, B. Wildemann, 'Spinal amaurosis' (1841). On the early contribution of Edward Hocken to the concept of neuromyelitis optica, J. Neurol. 261 (2014) 400–404.
[15] S. Jarius, B. Wildemann, Devic's disease before Devic: bilateral optic neuritis and simultaneous myelitis in a young woman (1874), J. Neurol. Sci. 358 (2015) 419–421.
[16] S. Jarius, B. Wildemann, Devic's disease before Devic: on the contribution of Friedrich Albin Schanz (1863-1923), J. Neurol. Sci. 379 (2017) 99–102.
[17] S. Jarius, A.B. Wuthenow, B. Wildemann, The first Japanese report on neuromyelitis optica rediscovered: acute bilateral blindness, tetraparesis and respiratory insufficiency in a 35-year-old man (1891), J. Neurol. Sci. 395 (2018) 121–125.
[18] S. Jarius, Wildemann B: An early British case of neuromyelitis optica (1850), BMJ 345 (2012) e6430.
[19] V.A. Lennon, T.J. Kryzer, S.J. Pittock, A.S. Verkman, S.R. Hinson, IgG marker of optic-spinal multiple sclerosis binds to the aquaporin-4 water channel, J. Exp. Med. 202 (2005) 473–477.
[20] V.A. Lennon, D.M. Wingerchuk, T.J. Kryzer, S.J. Pittock, C.F. Lucchinetti, K. Fujihara, I. Nakashima, B.G. Weinshenker, A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis, Lancet 364 (2004) 2106–2112.
[21] S. Jarius, F. Paul, D. Franciotta, P. Waters, F. Zipp, R. Hohlfeld, A. Vincent, B. Wildemann, Mechanisms of disease: Aquaporin-4 antibodies in neuromyelitis optica, Nat. Clin. Pract. Neurol. 4 (2008) 202–214.
[22] S. Jarius, B. Wildemann, AQP4 antibodies in neuromyelitis optica: diagnostic and pathogenetic relevance, Nat. Rev. Neurol. 6 (2010) 383–392.
[23] S. Jarius, B. Wildemann, Aquaporin-4 antibodies (NMO-IgG) as a serological marker of neuromyelitis optica: a critical review of the literature, Brain Pathol. 23 (2013) 661–683.
[24] S. Jarius, C. Probst, K. Borowski, D. Franciotta, B. Wildemann, W. Stoecker, K.P. Wandinger, Standardized method for the detection of antibodies to aquaporin-4 based on a highly sensitive immunofluorescence assay employing

recombinant target antigen, J. Neurol. Sci. 291 (2010) 52–56.
[25] D.M. Wingerchuk, B. Banwell, J.L. Bennett, P. Cabre, W. Carroll, T. Chitnis, J. de Seze, K. Fujihara, B. Greenberg, A. Jacob, et al., International consensus diagnostic criteria for neuromyelitis optica spectrum disorders, Neurology 85 (2015) 177–189.
[26] S. Mader, V. Gredler, K. Schanda, K. Rostasy, I. Dujmovic, K. Pfaller, A. Lutterotti, S. Jarius, F. Di Pauli, B. Kuenz, et al., Complement activating antibodies to myelin oligodendrocyte glycoprotein in neuromyelitis optica and related disorders, J. Neuroinflammation 8 (2011) 184.
[27] S. Jarius, F. Paul, O. Aktas, N. Asgari, R.C. Dale, J. de Seze, D. Franciotta, K. Fujihara, A. Jacob, H.J. Kim, et al., MOG encephalomyelitis: international recommendations on diagnosis and antibody testing, J. Neuroinflammation 15 (2018) 134.
[28] N. Borisow, M. Mori, S. Kuwabara, M. Scheel, F. Paul, Diagnosis and treatment of NMO Spectrum disorder and MOG-encephalomyelitis, Front. Neurol. 9 (2018) 888.
[29] R. Narayan, A. Simpson, K. Fritsche, S. Salama, S. Pardo, M. Mealy, F. Paul, M. Levy, MOG antibody disease: a review of MOG antibody seropositive neuromyelitis optica spectrum disorder, Mult. Scler. Relat. Disord. 25 (2018) 66–72.
[30] S. Jarius, I. Kleiter, K. Ruprecht, N. Asgari, K. Pitarokoili, N. Borisow, M. Hümmert, C. Trebst, F. Pache, A. Winkelmann, et al., MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 3: Brainstem involvement - frequency, presentation and outcome, J. Neuroinflammation (2016), https://doi.org/10.1186/s12974-016-0719-z.
[31] S. Jarius, K. Ruprecht, I. Kleiter, N. Borisow, N. Asgari, K. Pitarokoili, F. Pache, O. Stich, L. Beume, M.W. Hümmert, et al., MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 2: Epidemiology, clinical presentation, radiological and laboratory features, treatment responses, and long-term outcome, J. Neuroinflammation (2016), https://doi.org/10.1186/s12974-016-0718-0.
[32] S. Jarius, K. Ruprecht, I. Kleiter, N. Borisow, N. Asgari, K. Pitarokoili, F. Pache, O. Stich, L. Beume, M.W. Hümmert, et al., MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 1: Frequency, syndrome specificity, influence of disease activity, long-term course, association with AQP4-IgG, and origin, J. Neuroinflammation (2016), https://doi.org/10.1186/s12974-016-0717-1.
[33] F. Pache, H. Zimmermann, J. Mikolajczak, S. Schumacher, A. Lacheta, F.C. Oertel, J. Bellmann-Strobl, S. Jarius, B. Wildemann, M. Reindl, et al., MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 4: afferent visual system damage after optic neuritis in MOG-IgG-seropositive versus AQP4-IgG-seropositive patients, J. Neuroinflammation 13 (2016) 282.
[34] M. Reindl, S. Jarius, K. Rostasy, T. Berger, Myelin oligodendrocyte glycoprotein antibodies: how clinically useful are they? Curr. Opin. Neurol. 30 (2017) 295–301.
[35] Y. Kuroiwa, A. Igata, K. Itahara, S. Koshijima, T. Tsubaki, Nationwide survey of multiple sclerosis in Japan. Clinical analysis of 1,084 cases, Neurology 25 (1975) 845–851.
[36] S. Jarius, K. Ruprecht, B. Wildemann, T. Kuempfel, M. Ringelstein, C. Geis, I. Kleiter, C. Kleinschnitz, A. Berthele, J. Brettschneider, et al., Contrasting disease patterns in seropositive and seronegative neuromyelitis optica: a multicentre study of 175 patients, J. Neuroinflammation 9 (2012) 14.
[37] J.J. Chen, E.P. Flanagan, J. Jitprapaikulsan, A.S.S. Lopez-Chiriboga, J.P. Fryer, J.A. Leavitt, B.G. Weinshenker, A. McKeon, J.M. Tillema, V.A. Lennon, et al., Myelin oligodendrocyte glycoprotein antibody-positive optic neuritis: clinical characteristics, radiologic clues, and outcome, Am J. Ophthalmol. 195 (2018) 8–15.
[38] S. Ramanathan, S. Mohammad, E. Tantsis, T.K. Nguyen, V. Merheb, V.S.C. Fung, O.B. White, S. Broadley, J. Lechner-Scott, S. Vucic, et al., Clinical course, therapeutic responses and outcomes in relapsing MOG antibody-associated demyelination, J. Neurol. Neurosurg. Psychiatry 89 (2018) 127–137.
[39] S. Ramanathan, K. Prelog, E.H. Barnes, E.M. Tantsis, S.W. Reddel, A.P. Henderson, S. Vucic, M.P. Gorman, L.A. Benson, G. Alper, et al., Radiological differentiation of optic neuritis with myelin oligodendrocyte glycoprotein antibodies, aquaporin-4 antibodies, and multiple sclerosis, Mult. Scler. 22 (2016) 470–482.
[40] S. Jarius, I. Metz, F.B. Konig, K. Ruprecht, M. Reindl, F. Paul, W. Bruck, B. Wildemann, Screening for MOG-IgG and 27 other anti-glial and anti-neuronal autoantibodies in 'pattern II multiple sclerosis' and brain biopsy findings in a MOG-IgG-positive case, Mult. Scler. 22 (2016) 1541–1549.
[41] F.B. Konig, B. Wildemann, S. Nessler, D. Zhou, B. Hemmer, I. Metz, H.P. Hartung, B.C. Kieseier, W. Bruck, Persistence of immunopathological and radiological traits in multiple sclerosis, Arch. Neurol. 65 (2008) 1527–1532.
[42] M. Spadaro, L.A. Gerdes, M.C. Mayer, B. Ertl-Wagner, S. Laurent, M. Krumbholz, C. Breithaupt, T. Hogen, A. Straube, A. Giese, et al., Histopathology and clinical course of MOG-antibody-associated encephalomyelitis, Ann. Clin. Transl. Neurol. 2 (2015) 295–301.
[43] J.J. Wang, Z. Jaunmuktane, C. Mummery, S. Brandner, S. Leary, S.A. Trip, Inflammatory demyelination without astrocyte loss in MOG antibody-positive NMOSD, Neurology 87 (2016) 229–231.
[44] M.S. Weber, T. Derfuss, I. Metz, W. Bruck, Defining distinct features of anti-MOG antibody associated central nervous system demyelination, Ther. Adv. Neurol. Disord. 11 (2018) (1756286418762083).
[45] D.M. Bourneville, L. Guérard, De la sclérose en plaques disséminées, Delahay, Paris, 1869.
[46] S. Jarius, K. Ruprecht, I. Kleiter, N. Borisow, N. Asgari, K. Pitarokoili, F. Pache, O. Stich, L.A. Beume, M.W. Hummert, et al., MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 2: Epidemiology, clinical presentation, radiological and laboratory features, treatment responses, and long-term outcome, J. Neuroinflammation 13 (2016) 280.
[47] D. Biotti, F. Bonneville, E. Tournaire, X. Ayrignac, C.C. Dalliere, L. Mahieu, C. Vignal, C. Dulau, B. Brochet, A. Ruet, et al., Optic neuritis in patients with anti-MOG antibodies spectrum disorder: MRI and clinical features from a large multicentric cohort in France, J. Neurol. 264 (2017) 2173–2175.
[48] A.R. Lee, M.A. El-Dairi, Anti-myelin oligodendrocyte glycoprotein optic neuritis or neuroretinitis? JAMA Ophthalmol. 136 (2018) e182928.
[49] F.C. Moura, D.K. Sato, C.M. Rimkus, S.L. Apostolos-Pereira, L.M. de Oliveira, C.C. Leite, K. Fujihara, M.L. Monteiro, D. Callegaro, Anti-MOG (myelin oligodendrocyte glycoprotein)-positive severe optic neuritis with optic disc Ischaemia and macular star, Neuroophthalmology 39 (2015) 285–288.
[50] J.S. George, M.I. Leite, J.L. Kitley, N. Jones, N. Cortes, M. Donati, B.N. Matthews, D. Calladine, C. Hillier, I.H. Yusuf, et al., Opportunistic infections of the retina in patients with aquaporin-4 antibody disease, JAMA Neurol. 71 (2014) 1429–1432.
[51] J.L. Bennett, J. de Seze, M. Lana-Peixoto, J. Palace, A. Waldman, S. Schippling, S. Tenembaum, B. Banwell, B. Greenberg, M. Levy, et al., Neuromyelitis optica and multiple sclerosis: seeing differences through optical coherence tomography, Mult. Scler. 21 (2015) 678–688.
[52] F.C. Oertel, J. Havla, A. Roca-Fernandez, N. Lizak, H. Zimmermann, S. Motamedi, N. Borisow, O.B. White, J. Bellmann-Strobl, P. Albrecht, et al., Retinal ganglion cell loss in neuromyelitis optica: a longitudinal study, J. Neurol. Neurosurg. Psychiatry 89 (2018) 1259–1265.
[53] F.C. Oertel, H. Zimmermann, F. Paul, A.U. Brandt, Optical coherence tomography in neuromyelitis optica spectrum disorders: potential advantages for individualized monitoring of progression and therapy, EPMA J. 9 (2018) 21–33.
[54] F.C. Oertel, J. Kuchling, H. Zimmermann, C. Chien, F. Schmidt, B. Knier, J. Bellmann-Strobl, T. Korn, M. Scheel, A. Klistorner, et al., Microstructural visual system changes in AQP4-antibody-seropositive NMOSD, Neurol. Neuroimmunol. Neuroinflamm. 4 (2017) e334.
[55] S.A. Cross, D.R. Salomao, J.E. Parisi, T.J. Kryzer, E.A. Bradley, J.A. Mines, B.L. Lam, V.A. Lennon, Paraneoplastic autoimmune optic neuritis with retinitis defined by CRMP-5-IgG, Ann. Neurol. 54 (2003) 38–50.
[56] F. Ducray, R. Roos-Weil, P.Y. Garcia, J. Slesari, O. Heinzlef, D. Chatelain, P. Toussaint, E. Roullet, J. Honnorat, Devic's syndrome-like phenotype associated with thymoma and anti-CV2/CRMP5 antibodies, J. Neurol. Neurosurg. Psychiatry 78 (2007) 325–327.
[57] S. Jarius, K.P. Wandinger, K. Borowski, W. Stoecker, B. Wildemann, Antibodies to CV2/CRMP5 in neuromyelitis optica-like disease: case report and review of the literature, Clin. Neurol. Neurosurg. 114 (2012) 331–335.
[58] S. Jarius, C. Jacobi, J. de Seze, H. Zephir, F. Paul, D. Franciotta, P. Rommer, S. Mader, I. Kleiter, M. Reindl, et al., Frequency and syndrome specificity of antibodies to aquaporin-4 in neurological patients with rheumatic disorders, Mult. Scler. 17 (2011) 1067–1073.
[59] J. Zavada, P. Nytrova, K.P. Wandinger, S. Jarius, R. Svobodova, C. Probst, V. Peterova, D. Tegzova, K. Pavelka, J. Vencovsky, Seroprevalence and specificity of NMO-IgG (anti-aquaporin 4 antibodies) in patients with neuropsychiatric systemic lupus erythematosus, Rheumatol. Int. 33 (2013) 259–263.
[60] R. Bergamaschi, S. Jarius, M. Robotti, A. Pichiecchio, B. Wildemann, G. Meola, Two cases of benign neuromyelitis optica in patients with celiac disease, J. Neurol. 256 (2009) 2097–2099.
[61] K.P. Wandinger, M. Stangel, T. Witte, P. Venables, P. Charles, S. Jarius, B. Wildemann, C. Probst, C. Iking-Konert, M. Schneider, Autoantibodies against aquaporin-4 in patients with neuropsychiatric systemic lupus erythematosus and primary Sjogren's syndrome, Arthritis Rheum. 62 (2010) 1198–1200.
[62] N. Asgari, S. Jarius, H. Laustrup, H.P. Skejoe, S.T. Lillevang, B.G. Weinshenker, A. Voss, Aquaporin-4-autoimmunity in patients with systemic lupus erythematosus: a predominantly population-based study, Mult. Scler. 24 (2018) 331–339.
[63] V.M. Shivamurthy, S. Ganesan, A. Khan, N. Hussain, A.V. Sridhar, Acute longitudinal myelitis as the first presentation in a child with systemic lupus erythematosus, J. Pediatr. Neurosci. 8 (2013) 150–153.
[64] Y. Benmoh, A. Elbekal, S. Hamid, M. Ajamat, M. Khalidi, N. Hjira, A. Bourazza, Longitudinally extensive transverse myelitis revealing systemic lupus erythematosus: a case report and literature review, J. Neurol. Neurophysiol. 9 (2018) 1000469.
[65] G. Akdal, H.E. Toydemir, A.O. Saatci, U. Uygunoglu, B. Altunrende, S. Saip, A. Yaman, P. Keskinoglu, S.G. Yilmaz, N. Celebisoy, et al., Characteristics of optic neuropathy in Behcet disease, Neurol. Neuroimmunol. Neuroinflamm. 5 (2018) e490.
[66] D. Dubey, S.J. Pittock, K.N. Krecke, P.P. Morris, E. Sechi, N.L. Zalewski, B.G. Weinshenker, E. Shosha, C.F. Lucchinetti, J.P. Fryer, et al., Clinical, radiologic, and prognostic features of myelitis associated with myelin oligodendrocyte glycoprotein autoantibody, JAMA Neurol. 21 (2018 Dec), https://doi.org/10.1001/jamaneurol.2018.4053 (epub ahead of print).
[67] D.K. Sato, D. Callegaro, M.A. Lana-Peixoto, P.J. Waters, F.M. de Haidar Jorge, T. Takahashi, I. Nakashima, S.L. Apostolos-Pereira, N. Talim, R.F. Simm, et al., Distinction between MOG antibody-positive and AQP4 antibody-positive NMO spectrum disorders, Neurology 82 (2014) 474–481.
[68] C. Trebst, P. Raab, E.V. Voss, P. Rommer, M. Abu-Mugheisib, U.K. Zettl, M. Stangel, Longitudinal extensive transverse myelitis—it's not all neuromyelitis optica, Nat. Rev. Neurol. 7 (2011) 688–698.
[69] J.L. Kitley, M.I. Leite, J.S. George, J.A. Palace, The differential diagnosis of longitudinally extensive transverse myelitis, Mult. Scler. 18 (2012) 271–285.
[70] E.P. Flanagan, T.J. Kaufmann, K.N. Krecke, A.J. Aksamit, S.J. Pittock, B.M. Keegan, C. Giannini, B.G. Weinshenker, Discriminating long myelitis of neuromyelitis optica from sarcoidosis, Ann. Neurol. 79 (2016) 437–447.
[71] S. Jarius, F.B. Konig, I. Metz, K. Ruprecht, F. Paul, W. Bruck, B. Wildemann,

Pattern II and pattern III MS are entities distinct from pattern I MS: evidence from cerebrospinal fluid analysis, J. Neuroinflammation 14 (2017) 171.
[72] J.J. Dejerine, A. Dejerine-Klumpke, Anatomie des centres nerveux. Tome premier, Rueff, Paris, 1895.
[73] W.F. Robertson, On a new method of obtaining a black reaction in certain tissue-elements of the central nervous system (platinum method), Scott. Med. Surg. 4 (1899) 23–30.
[74] W.F. Robertson, Morbid conditions of the neuroglia, in: Robertson WFE (Ed.), Pathology in Relation to Mental Diseases, Clay, Edinburgh, 1900, pp. 164–193.
[75] P. del Río-Hortega, Estudios sobre la neurologia. La glía de escasas radiaciones (oligodendroglía), Boletín de la Real Sociedad Española de Historia Natural 21 (1921) 63–92.
[76] P. del Río-Hortega, El “tercer elemento” de los centros nerviosos, Bol. Soc. Esp. Biol. 9 (1919) 68–82.
[77] A.I. Boullerne, The history of myelin, Exp. Neurol. 283 (2016) 431–445.
[78] H.J. Kim, F. Paul, M.A. Lana-Peixoto, S. Tenembaum, N. Asgari, J. Palace, E.C. Klawiter, D.K. Sato, J. de Seze, J. Wuerfel, et al., MRI characteristics of neuromyelitis optica spectrum disorder: an international update, Neurology 84 (2015) 1165–1173.
[79] N.R. Miller, N.J. Newman, V. Biousse, J.B. Kerrison, Walsh and Hoyt's Clinical Neuro-Ophthalmology, vol. 1, Philadelpha, Lippincott Williams & Wilkons, 2005.
[80] L. Chilver-Stainer, U. Fischer, M. Hauf, C.A. Fux, M. Sturzenegger, Syphilitic myelitis: rare, nonspecific, but treatable, Neurology 72 (2009) 673–675.
[81] S. Jarius, F. Paul, K. Ruprecht, B. Wildemann, Low vitamin B12 levels and gastric parietal cell antibodies in patients with aquaporin-4 antibody-positive neuromyelitis optica spectrum disorders, J. Neurol. 259 (2012) 2743–2745.
[82] C.M. McClelland, G.P. Van Stavern, A.C. Tselis, Leber hereditary optic neuropathy mimicking neuromyelitis optica, J. Neuroophthalmol. 31 (2011) 265–268.
[83] G.G. Kovacs, R. Hoftberger, K. Majtenyi, R. Horvath, P. Barsi, S. Komoly, H. Lassmann, H. Budka, G. Jakab, Neuropathology of white matter disease in Leber's hereditary optic neuropathy, Brain 128 (2005) 35–41.
[84] W. Shiraishi, S. Hayashi, T. Kamada, N. Isobe, R. Yamasaki, H. Murai, Y. Ohyagi, J. Kira, A case of neuromyelitis optica harboring both anti-aquaporin-4 antibodies and a pathogenic mitochondrial DNA mutation for Leber's hereditary optic neuropathy, Mult. Scler. 20 (2014) 258–260.
[85] L.M. Simao, Neuromyelitis optica antibody in Leber hereditary optic neuropathy: case report, Arq. Bras. Oftalmol. 75 (2012) 280–282.
[86] N. Usmani, M. McCarthy, K.W. Rammohan, M.R. Ortega, Fulminant myelitis with NMO IgG antibody following treatment with interferon alpha, J. Neurol. 261 (2014) 240–241.
[87] R. Ben Aoun, H. Benrhouma, H. Klaa, T. Ben Younes, C. Drissi, A. Rouissi, M. Ben Ahmed, I. Kraoua, I. Ben Youssef-Turki, Neuromyelitis optica spectrum disorder with spinal involvement including conus medullaris lesions with anti-aquaporin-4 antibody: a pediatric case and literature review, Ann. Ped. 1 (2019) 1011.
[88] A. McKeon, V.A. Lennon, T. Lotze, S. Tenenbaum, J.M. Ness, M. Rensel, N.L. Kuntz, J.P. Fryer, H. Homburger, J. Hunter, et al., CNS aquaporin-4 autoimmunity in children, Neurology 71 (2008) 93–100.
[89] A. Peng, J. Cai, W. Lai, L. Zhang, X. Qiu, X. Zhu, S. He, L. Chen, Autoimmune Aquaporin-4 Channelopathy presented with psychiatric symptoms: a case report, Neuropsychiatry (Lond.) 8 (2018) 801–807.
[90] P. Moore, A. Methley, C. Pollard, K. Mutch, S. Hamid, L. Elsone, A. Jacob, Cognitive and psychiatric comorbidities in neuromyelitis optica, J. Neurol. Sci. 360 (2016) 4–9.
[91] F. Blanc, H. Zephir, C. Lebrun, P. Labauge, G. Castelnovo, M. Fleury, F. Sellal, C. Tranchant, K. Dujardin, P. Vermersch, J. de Seze, Cognitive functions in neuromyelitis optica, Arch. Neurol. 65 (2008) 84–88.
[92] D.M. Wingerchuk, B.G. Weinshenker, The emerging relationship between neuromyelitis optica and systemic rheumatologic autoimmune disease, Mult. Scler. 18 (2012) 5–10.
[93] S. Jarius, C. Jacobi, J. de Seze, H. Zephir, F. Paul, D. Franciotta, P. Rommer, S. Mader, I. Kleiter, M. Reindl, et al., Frequency and syndrome specificity of antibodies to aquaporin-4 in neurological patients with rheumatic disorders. Mult Scler J (in press), Mult. Scler. 17 (2011) 1067–1073.
[94] J.M. Seok, M. Choi, E.B. Cho, H.L. Lee, B.J. Kim, K.H. Lee, P. Song, E.Y. Joo, J.H. Min, Fatigue in patients with neuromyelitis optica spectrum disorder and its impact on quality of life, PLoS One 12 (2017) e0177230.
[95] C. Fernandez-Carbonell, D. Vargas-Lowy, A. Musallam, B. Healy, K. McLaughlin, K.W. Wucherpfennig, T. Chitnis, Clinical and MRI phenotype of children with MOG antibodies, Mult. Scler. 22 (2016) 174–184.
[96] S. Asseyer, F. Schmidt, C. Chien, M. Scheel, K. Ruprecht, J. Bellmann-Strobl, A.U. Brandt, F. Paul, Pain in AQP4-IgG-positive and MOG-IgG-positive neuromyelitis optica spectrum disorders, Mult. Scler. J. Exp. Transl. Clin. 4 (2018) (2055217318796684).
[97] Y. Guo, V.A. Lennon, B.F. Popescu, C.K. Grouse, J. Topel, M. Milone, H. Lassmann, J.E. Parisi, S.J. Pittock, D. Stefoski, et al., Autoimmune aquaporin-4 myopathy in neuromyelitis optica spectrum, JAMA Neurol. 71 (2014) 1025–1029.
[98] L. Dennis, Hatting. As affecting the health of operatives, Report of the Board of Health of the State of New Jersey, 2 1878, pp. 67–85.
[99] R.P. Wedeen, Were the hatters of New Jersey "mad"? Am. J. Ind. Med. 16 (1989) 225–233.
[100] P.M. Roos, L. Dencker, Mercury in the spinal cord after inhalation of mercury, Basic Clin. Pharmacol. Toxicol. 111 (2012) 126–132.
[101] F. Bakir, H. Rustam, S. Tikriti, S.F. Al-Damluji, H. Shihristani, Clinical and epidemiological aspects of methylmercury poisoning, Postgrad. Med. J. 56 (1980) 1–10.
[102] S.F. Al-Damluji, Intoxication due to alkylmercury-treated seed—1971-72 outbreak in Iraq: clinical aspects, Bull. World Health Organ. 53 (Suppl) (1976) 65–81.
[103] S. Sabelaish, G. Hilmi, Ocular manifestations of mercury poisoning, Bull. World Health Organ. 53 (Suppl) (1976) 83–86.
[104] K. Patterson, E. Iglesias, M. Nasrallah, V. Gonzalez-Alvarez, M. Sunol, J. Anton, et al., Anti-MOG encephalitis mimicking small vessel CNS vasculitis, Neurol. Neuroimmunol. Neuroinflamm. 6 (2) (2019) e538.
[105] R. Hoftberger, E. Gelpi, Diagnostic challenges and pitfalls of myelin oligodendrocyte glycoprotein antibody-associated demyelination: Lessons from neuropathology, Neurol. Neuroimmunol. Neuroinflamm. 6 (2) (2019) e544.