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Clinical short communication

# The first Japanese report on neuromyelitis optica rediscovered: acute bilateral blindness, tetraparesis and respiratory insufficiency in a 35-year-old man (1891)

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ABSTRACT

The term 'neuromyelitis optica' (NMO, Devic syndrome) is used to refer to a syndrome characterized by optic neuritis and myelitis. For many decades NMO was classified as a clinical variant of multiple sclerosis (MS). Recent research has shown, however, that NMO differs from MS in terms of immunopathogenesis, clinical presentation, and optimum treatment. In most cases, NMO is caused by autoantibodies to aquaporin-4 or myelin oligodendrocyte glycoprotein. While the history of classic MS has been studied extensively, only relatively little is known about the early history of NMO. Although NMO is considered to be much more prevalent among Asian than among European patients with CNS demyelination, all early reports of NMO reviewed by Eugène Devic and Fernand Gault in their seminal 1894 review and all other reports from the 19th century re-discovered by us over the past years related cases of NMO in patients of European descent. Here, we would like to draw the attention to an early report on NMO in a Japanese patient, published by Tanemichi Aoyama (1859–1917), one of the most eminent physicians of the Meiji period, an era characterized by a Western-style revolution in Japanese medicine. The report was published in 1891, i.e. 3 years before Devic and Gault's disease defining study on NMO. To the best of our knowledge, this is the earliest report on an Asian patient with NMO. We give an English translation of the original Japanese report written in *bungo* (pre-modern Japanese) and discuss the case both in the light of current knowledge on NMO and from a historical perspective.

## 1. Introduction

Neuromyelitis optica (Devic syndrome, NMO) is a rare syndrome characterized by simultaneous or consecutive optic neuritis and myelitis [1–3]. Syndrome-specific, pathogenic immunoglobulin G (IgG) autoantibodies were first discovered in patients with NMO in 2004 and subsequently shown to target the water-channel protein aquaporin-4 (AQP4) [4–8]. In a subset of AQP4-IgG-negative patients, IgG antibodies to myelin oligodendrocyte glycoprotein (MOG) were recently shown to be involved in the pathogenesis of NMO [9–15]. NMO has substantial phenotypic overlap with multiple sclerosis (MS) but may take a more severe disease course. If untreated, NMO can lead to blindness and/or tetraparesis. While the history of MS has been studied intensively, relatively little is known about the history of NMO [16]. In recent years, we have rediscovered a number of very early cases of NMO, all published prior to Eugène Devic (1858–1930) and Fernand Gault's (1873–1936) seminal and disease-defining 1894 review in which the term "neuromyelitis optica" was first coined. Although NMO is now considered to be more common in Asian countries, the disease was first described exclusively in patients of European descent, probably reflecting the tremendous progress clinical neurology made in the Western hemisphere in the second half of the 19th century – the era of Jean-Martin Charcot (1825–1893), William Richard Gowers (1845–1915) and Wilhelm Erb (1840–1921).

Here we re-present a widely forgotten early report on a Japanese patient with NMO, which appeared in 1891 in *Journal of the Tokyo Medical Association (Tôkyô Igaku-kai Zasshi)* [17] and was authored by one of the most eminent Japanese physicians of the late 19th and early 20th century, Tanemichi Aoyama (1859–1917) (Figs. 1 and 2) [18,19]. We came across this case when performing a bibliographic search for articles citing an 1889 report on a German patient with possible NMO. To the best of our knowledge, this is the first published case of NMO in an Asian country. In addition, we discuss the contemporary stance on NMO and point to the important role played by Tanemichi Aoyama in

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**Fig. 1.** Tanemichi Aoyama (青山 胤) (1859–1917).

the flowering of Japanese clinical medicine and neurology of Japan at that time.

## 2. Case report

On June 1st, 1891, the patient, a 35-year-old male sculptor, caught a common cold with severe fever and chills. Eight days later, he experienced severe visual loss (finger counting only) in the left eye upon waking up and later developed unusual fatigue. The next morning, he could neither move nor feel his left leg. Later that day, he suffered sensory loss and subsequently paresis also of the right leg, together with vertebral spasms, urinary incontinence and obstipation. In parallel, visual acuity declined also in the right eye, accompanied by severe ocular pain upon eye movement and fluctuating yet permanent periocular and occipital headache. When he awoke the next morning, light perception had completely vanished in both eyes. Physical examination revealed a complete sensory level at T6, sensorimotor paralysis of the lower extremities and complete bilateral blindness with missing light and convergence reaction, as well as signs of acute infection (fever, tachycardia, tachypnoea, swelling of the lymph nodes, coated tongue). Ophthalmoscopy revealed signs of possible papillitis (hyperaemia, mild blurring). Two days later, symptoms worsened with tetraparesis, a sensory level at C4/5, and intestinal incontinence. In addition, decubitus ulcers were noted as well as signs of lung oedema and respiratory distress. In the afternoon of the same day, the patient died of respiratory insufficiency. No signs of either cognitive decline or cranial nerve involvement were present over the entire disease course. No autopsy was performed. The final diagnosis was “acute myelitis with simultaneous optic neuritis”, based on the symptoms and time course.

## 3. Discussion

We recently pointed out that Devic and Gault, in their disease-defining review of NMO, overlooked numerous previously published cases [20–28], probably owing to the restricted bibliographic resources of the time. All of these cases preceded Devic and Gault's own case by years or even decades: As early as 1841, the young Cornish ophthalmologist Edward Octavius Hocken (1820–1845) published a case of spinal cord inflammation and amaurosis in *The Lancet* and suggested that the association was not by chance but might share the same pathogenesis [25]. Shortly afterwards, in 1844, the Genoese physician Giovanni Battista Pescetto (1806–1884) described a 42-year-old Italian man with symptoms highly suggestive of NMO [22]. In 1850, Christopher Mercer Durrant (1814–1901), a physician from Suffolk, reported on an English patient with acute tetraparesis and (partly reversible) bilateral amaurosis in the precursor of the *British Medical Journal*, the *Provincial Medical and Surgical Journal* [23]. Another British report overlooked by Devic and Gault, describing the case of a 17-year-old girl with bilateral optic neuritis and longitudinally extensive transverse myelitis, was published by the famous neurologist and neuroanatomist Jacob Augustus Lockhart Clarke (1817–1880), eponym of Clarke's column, in *The Lancet* in 1862 [20]. In 1876, the Polish physician Adolf Wurst (1848–unknown) reported on a 30-year-old women afflicted by subacute simultaneous bilateral optic neuritis with papilloedema, bilateral blindness and transverse myelitis, the first published case of possible NMO outside Western Europe [27]. Finally, a 1804 report by Antoine Portal (1742–1832), first physician to Louis XVIII and founding and lifelong president of the *Académie Nationale de Médecine*, deserves to be mentioned here: it represents the first known account of visual loss in a patient with spinal cord inflammation but no brain pathology in the Western literature [21].

Of note, all of the early reports rediscovered and previously republished by us [20–28], as well as those reviewed by Devic and Gault in their seminal 1894 study described patients of European descent [29–31]. Here, we point to a forgotten report on a Japanese patient with simultaneous myelitis and bilateral ON, which, to the best of our knowledge, is the earliest report from an Asian country yet identified [18]. Asian patients with demyelinating diseases are considered to have NMO much more often than their European counterparts. Indeed, many patients with optic neuritis and myelitis were classified as “opticospinal multiple sclerosis” (OSMS) in Japan in the past. However, recent studies have demonstrated that the majority of Japanese patients classified as “OSMS” actually have disorders distinct from MS, namely AQP4-IgG-positive or MOG-IgG-positive NMO [32]. In line with this finding, the patient reported here showed typical signs of NMO such as bilateral ON and simultaneous occurrence of ON and myelitis, which is rare in MS. Similarly, the highly acute and severe disease course, featuring complete bilateral blindness, complete tetraparesis with total loss of bowel and bladder control, and respiratory insufficiency leading to the patient's death within 5 days of onset of neurological symptoms, is atypical for MS and strongly argues in favour of a diagnosis of NMO. Acute respiratory insufficiency due to high cervical myelitis or brainstem encephalitis is the most common cause of death in (untreated) patients with AQP4-IgG-positive NMO. Importantly, early treatment of attacks and the availability of new long-term immunosuppressive treatments have led to a substantial decline in mortality: in a recent large European study (median year of disease onset: 2004), only 9/175 (6%) patients with NMO had died after a median observation period of 57.5 months [1]. This compares to a survival rate of only 68% found in a 1999 North American study of patients with disease onset in the 1970s and 1980s [33]. The lack of signs or symptoms (except for headache) indicating brain involvement in Aoyama's case also argues against MS and in favour of NMO. Brain involvement is relatively rare in NMO, especially at disease onset ($< 50\%$), but frequently present in patients with MS [32–34]. The fact that Aoyama's patient was male does not rule out NMO. NMO indeed predominantly affects women. However, around 10% of all patients with AQP4-IgG-positive NMO and up to 30% of patients with seronegative NMO are men [1].

While simultaneous ON and myelitis, as observed in Aoyama's case, is highly suggestive of NMO, the disease often starts with either isolated ON or isolated longitudinally extensive transverse myelitis [1]. More rarely, signs or symptoms of isolated brainstem encephalitis or encephalitis mark the onset. These observations have given rise to the concept of neuromyelitis optica spectrum disorders (NMOSD), an umbrella term covering both NMO and its *formes frustes* [35,36].