Pediatric Neurology 96 (2019) 3–6

Contents lists available at ScienceDirect

Pediatric Neurology

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

Historical Vignette

So Dramatic They Could Never Be Overlooked: History of Pediatric Neuromyelitis Optica

Alison Christy, MD, PhD *

Pediatric Neurology, Providence Health & Services, Portland, Oregon

ARTICLE INFO

Article history:
Received 20 October 2018
Accepted 3 February 2019
Available online 10 February 2019

Keywords:
Neuromyelitis optica
History of neurology
Pediatric
Optic neuritis
Transverse myelitis

Background

Neuromyelitis optica (NMO) is a rare but severe demyelinating disease that preferentially affects the optic nerves and spinal cord and is associated with antibodies to aquaporin 4 or myelin oligodendrocyte glycoprotein. In 1894, Eugène Devic reviewed several patients with *neuro-myèlite optique aiguë* at the Congrès Français de Mèdecine in Lyon. That same year his doctoral student Fernand Gault published his thesis, *De la neuro-myèlite optique aiguë*.[1] Devic and Gault did not discover the co-occurrence of optic neuritis and spinal cord disease, but instead reviewed case reports from other physicians, including Sir Thomas Allbutt, inventor of the thermometer,[2,3] and Friedrich Schanz, who in 1893 described optic neuritis followed by transverse myelitis in a 19-year-old.[4,5] However, Devic systematically and thoroughly reviewed the known cases at the time, coining the term *neuromyelitis optica* and earning the eponym *Devic disease*.

Many of the earliest reported examples of NMO were found in prepubertal children, although only 4% of the NMO patients are pediatric. Between 1894 and 2000, fewer than 10 articles per year were published on the disease.[6] This literature search identified nine pediatric patients with NMO reported in six articles over the 18 years between 1927 and 1945 (Table).

The first reported pediatric case, one of the most severe, came from Gilbert M. Beck of Buffalo General Hospital in 1927. A 15-year-old girl presented with optic neuritis, "attacks of emesis," and lower extremity weakness. Symptoms remitted and recurred, and she exhibited autonomic instability. Autopsy revealed demyelination of the spinal cord, the optic nerves, and the optic chiasm. Beck noted that "normal areas of myelin seemed to melt away"[8] (Fig).

In 1934, Richard Perritt of Chicago described two patients: a 12-year-old boy with blindness and paralysis and a five-year-old girl with "lameness in one leg" and vision loss. Perritt, an ophthalmologist, noted that she cooperated with the examination and "the findings are of more value than those in the average child of five." Perritt lists various contemporary treatments including mercury, iodides, salicylates, strychnine, electrical therapy, and shaded lenses for photophobia.[9]

Dr. Sanford Gifford reported Perritt's cases again in 1937. He wrote "These cases are so dramatic that they could never be overlooked if a typical case has been seen before." He also writes "We have here condensed in a few weeks what happens in multiple sclerosis during the course of years."[10]

Two cases appeared in the international literature. In 1937, Shone described a seven-year-old girl in India presenting with blindness and lower limb paralysis.[11] In 1953, a similar six-year-old boy was reported in *Acta Pediatrica Espanola*.[12]

Disclosure: No disclosures.
Funding: This study is not industry sponsored.
Conflicts of interest: The author declares no conflicts of interest.
* Communications should be addressed to: Christy; Pediatric Neurology; Providence Health & Services; 9427 SW Barnes Rd, Suite 395; Portland, OR 97225.
E-mail address: alison.christy@providence.org.

https://doi.org/10.1016/j.pediatrneurol.2019.02.004
0887-8994/

TABLE.
A List of Nine Pediatric Patients Presenting Between 1926 and 1945[7]

Year of Publication, Author, Article	Age, Sex	Symptoms	Cerebrospinal Fluid Characteristics (with Original Units)	Treatment	Outcome
Beck, G.M. (1927)	15, F	Vomiting, then bilateral optic neuritis with visual auras, followed by leg weakness, hyperreflexia, and urinary and bowel incontinence	Cell count, 4 per cm^3; protein 0.04%	Silver-salvarsan (an arsenic compound used to treat syphilis)	Remission, then recurrence, with paralysis, autonomic instability and death; autopsy revealed demyelination of optic nerve, optic chiasm, and thoracic spinal cord
Perritt, R. (1934)	5, F	Bilateral optic neuritis after a "bad cold," followed by right lower extremity weakness with hyperreflexia	Opening pressure, normal; cell count, 92 per cm^3; glucose 50 mg/100 cm^3	Mercury, potassium iodide	Symptoms resolved with mild vision impairment in the right eye
Perritt, R. (1934)	12, M	Left optic neuritis, followed by right-sided paralysis with right optic neuritis	Not reported	Foreign protein therapy (no agreed definition; possibly immunoglobulin, may include other protein products*)	Symptoms resolved
Shone, S. (1940)	7, F	Bilateral blindness and sudden bilateral lower extremity paralysis, without loss of sensation	Cell count, 7 per cm^3; protein 30 mg; glucose 100 mg/100 cm^3, negative culture	Hexamine solution	Symptoms resolved in one month
No authors listed (1953). Un Caso de Oftalmomielitis Infantil	6, M	Flaccid paralysis with areflexia, sensory loss, and urinary retention, followed by vision loss and unilateral parotiditis	Cell count, 24 per cm^3; protein, 0.40 (no units given); glucose 0.80 (no units given); negative culture	Antibiotics, vitamins, IVIg	After one month, recurrence of both vision loss and paralysis, with recovery
Markham, J.W. and Otansek, F.J. (1954)	16, F	Diplopia and blurry vision, followed by ascending flaccid paralysis with areflexia, urinary incontinence, and constipation	White blood cells, 6 per cm^3; protein, 11 mg/100 mL, negative culture	Penicillin, sulfadiazine	Recurrence of both eye pain and weakness in legs one year later, with remission
Markham, J.W. and Otansek, F.J. (1954) (also reported in Walsh, F.B. (1935)	9, F	"Rapidly failing vision" and progressive ascending flaccid paralysis with hyporeflexia	Opening pressure 85 mm water; 1300 white blood cells per mm^3; protein 50 mgm.%, negative culture	Not reported	Death from "bulbar paralysis" (per Walsh, unable to swallow, intercostal muscles not functioning). Autopsy revealed liquification and demyelination of spinal cord
Markham, J.W. and Otansek, F.J. (1954) (also reported in Walsh, F.B., 1935)	9, F	Transverse myelitis, followed by dysarthria one year after onset, then right-sided optic neuritis	One white blood cell per mm^3; "sugar present"	Not reported	Continued spasticity of the lower extremities and nocturnal enuresis
Markham, J.W. and Otansek, F.J. (1954) (also reported in Walsh, F.B., 1935)	17, F	Rapid vision loss in both eyes leading to blindness in left eye; then two episodes of paraplegia and one of right eye blindness in the next year. Five years later, third attack of spastic paraplegia with urinary retention, Horner syndrome, and a sensory level at T3	120 mm water pressure, 34 cells, NPN 21 mgm.%, and sugar 20 mgm.%	Not reported	Craniotomy was performed to look for tumor, leading to left eye blindness. Six months after last episode vision was greatly impaired in the right eye, along with "marked residuals of transverse myelitis"

Abbreviations:
F = Female
IVIg = Intravenous immunoglobulin
M = Male
NPN = Non-protein nitrogen

Dr. James Markham and Dr. Frank Otenasek published a case series from the Johns Hopkins Hospital between 1925 and 1952.[13] This report highlights the prevalence of pediatric cases of NMO in the early literature: of the 10 cases recorded over 27 years, four (40%) presented under age 18 years.

Dr. Frank B. Walsh reported three of the Johns Hopkins cases in 1935, noting that two patients are under 10 years, which would be "an unusual age incidence for multiple sclerosis,"[14] the first mention of pediatric predominance in NMO.

In 1928, a 17-year-old girl presented with acute vision loss. Without modern head imaging, "a left frontal craniotomy was done and the chiasmal region explored," permanently blinding the left eye. Five years later, she developed transverse myelitis.[13]

In 1931, a nine-year-old girl presented with spastic paralysis and incontinence after illness, with optic neuritis two years later.[13,14] In 1932 Walsh, Markham, and Otensak described a nine-year-old girl who died 34 days after admission for bilateral blindness and paralysis. Autopsy revealed extensive involvement of the spinal cord, which was caudally "liquefied" and rostrally showed cavitations and demyelination[14] (Fig).

Markham and Otenasek described an additional patient in 1945, a 16-year-old who presented with blurred vision, and then leg weakness, which remitted and recurred.[13]

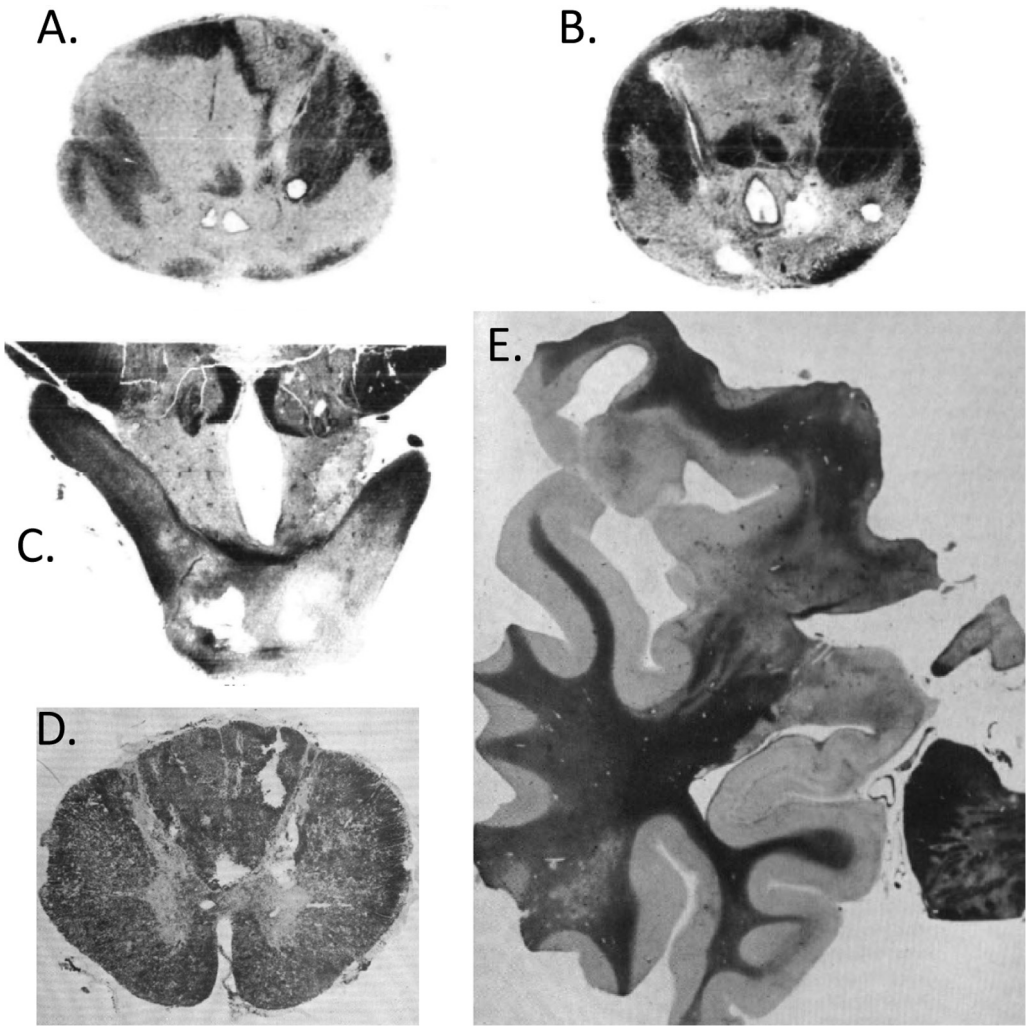

FIGURE. (A) Weigert stain of the sixth and (B) seventh thoracic segments of the spinal cord, with (C) superior portion of the optic chiasm, from autopsy of a 15-year-old patient described by Beck in a 1927 article, showing "massive demyelination, wholly unsystematized." (D) The eighth thoracic segment of the spinal cord, showing "macroscopic cavitations," and (E) complete demyelination (Spielmeyer stain) of the left half of the optic chiasm, from the autopsy of a nine-year-old patient, described by Walsh in 1935.

Discussion

Many early case reports of NMO were in children, and this is notable as the current incidence of NMO is low (from 0.053 to 0.40 per 100,000 people)[6] and only 4% of NMO cases are pediatric.[15]

The patients in the nine case reports reviewed here did not have imaging or antibody testing to confirm the diagnosis of NMO, but all fit the clinical criteria for NMO spectrum disorder,[15,16] with both optic neuritis and transverse myelitis. Only Beck's patient had vomiting concerning for area postrema syndrome, although several had symptoms localizing to the brainstem.

Some early examples of pediatric NMO may have been misdiagnosed. From 1917 to the late 1920s, many adults developed headache, lethargy, and coma, followed by post-encephalitic parkinsonism, termed *encephalitis lethargica* or von Economo disease. Children presented with irritability and lethargy, and psychiatric disturbances.[17,18] In 1920, C. P. Symonds reported two examples of "encephalitis lethargica with optic neuritis" in nine- and 10-year-old girls. Both had vomiting, paralysis and sensory loss, cerebrospinal fluid lymphocytosis, and bilateral optic neuritis. Both children recovered.[19] As optic neuritis was not otherwise associated with encephalitis lethargica, and neither children had lethargy, Symonds may have been describing pediatric NMO.

The pediatric prevalence in the literature may indicate that NMO more frequently affected the pediatric population between 1925 and 1945, possibly due to other circulating viruses or common childhood illnesses. Epidemics like encephalitis lethargica[17] demonstrate how inflammatory diseases can spike transiently and can present differently in children.

Children may feature prominently in the early literature as they are unlikely to have other causes of both optic neuritis and spinal cord disease. Adults with optic nerve and spinal cord disease may have been diagnosed with infection, trauma, or multiple sclerosis (MS) instead of NMO. Perritt notes that both neurosyphilis and malaria can cause NMO.[9]

NMO was considered a subtype of MS for many years, whereas case reports before 1940 distinguish between MS and NMO due to the severe demyelination seen in the latter. One 1942 discussion points out that "while NMO may occur in young children and even infants…multiple sclerosis does not occur at such an early age."[20] We know now that MS occurs at a rate of approximately 2.5 per 100,000 children, considerably higher than pediatric NMO.[21] However, the perception that relapsing-remitting symptoms in

children could not be MS may have increased attention to pediatric cases of NMO, making pediatric cases critical for the early characterization and understanding of NMO.

Acknowledgment

Jennifer L. Croft provided Spanish translations. Librarians Basia Delawska-Elliott and Kathryn Gibbs were instrumental in finding and providing articles for this research.

References

1. Gault F. "De La Neuromyélite Optique Aiguë." Thése: Faculté de Médecine et de Pharmacie. Alexandre Rey, Imprimeur de la Faculte de Médecine: Lyon; 1894.
2. Allbutt TC. On the ophthalmoscopic signs of spinal disease. Lancet. 1870;95:76–78.
3. Jarius S, Wildemann B. On the contribution of Thomas Clifford Allbutt, F.R.S., to the early history of neuromyelitis optica. J Neurol. 2013;260:100–104.
4. Jarius S, Wildemann B. Devic's disease before Devic: on the contribution of Friedrich Albin Schanz (1863-1923). J Neurol Sci. 2017;379:99–102.
5. Schanz F. Über Das Zusammenvorkommen von Neuritis Optica Und Myelitis Subacuta. Deutsche Medizinische Wochenschrift. 1893;19:615–617.
6. Marrie RA, Gryba C. The incidence and prevalence of neuromyelitis optica: a systematic review. Int J MS Care. 2013;15:113–118.
7. Cecil RL. Nonspecific protein therapy. J Am Med Assoc. 1935;105:1846–1854.
8. Beck GM. A case of diffuse myelitis associated with optic neuritis. Brain. 1927;50:687–703.
9. Perritt RA. Optic neuromyelitis, report of two cases. Arch Ophthalmol. 1934;11:492–497.
10. McKee SH, McNaughton FL. Neuromyelitis optica: a report of two cases. Trans Am Ophthalmol Soc. 1937;35:125–135.
11. Shone S. A case of neuromyelitis optica. Ind Med Gaz. 1940;75:548–549.
12. Un Caso de Oftalmomielitis Infantile. Acta Pediatrica Espanola. 1953;11:625–628.
13. Markham JW, Otenasek FJ. Neuromyelitis optica simulating spinal cord tumor; report of a case, with a review of nine additional cases. AMA Arch Neurol Psychiatry. 1954;72:758–763.
14. Walsh F. Neuromyelitis optica: an anatomical-pathological study of one case; clinical studies of three additional cases. Bull Johns Hopkins Hosp. 1935;56:183.
15. Chitnis T, Ness J, Krupp L, et al. Clinical features of neuromyelitis optica in children: US network of pediatric MS centers report. Neurology. 2016;86:245–252.
16. Wingerchuk, Dean M, Banwell B, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology. 2015;85:177–189.
17. Hoffman LA, Vilensky JA. Encephalitis lethargica: 100 years after the epidemic. Brain. 2017;140:2246–2251.
18. Vilensky JA, Foley P, Gilman S. Children and encephalitis lethargica: a historical review. Pediatr Neurol. 2007;37:79–84.
19. Symonds CP. Optic neuritis in encephalitis lethargica. Lancet. 1920;196:1245–1247.
20. Putnam TJ, Forster FM. Neuromyelitis optica: its relation to multiple sclerosis. Trans Am Neurol Assoc. 1942;68:20–25.
21. Gadoth N. Multiple sclerosis in children. Brain Dev. 2003;25:229–232.