Clinical Reasoning: A 6-Year-Old Girl With Right-Sided Pain and Weakness

Cristina M. Gaudioso, MD,* Rachel Zolno, MD,* Anne Wagner, RN, and Soe Mar, MD

Neurology® 2023;100:97-102. doi:10.1212/WNL.0000000000201481

Correspondence
Dr. Gaudioso
gaudioso@wustl.edu

Abstract

We outline the case of a 6-year-old girl presenting with a 2-week course of waxing and waning neurologic symptoms, including right-sided pain, weakness, dizziness, and difficulty walking. Her examination was notable for right-sided weakness, hyperreflexia, and dysmetria. Diagnostic evaluation was significant for MRI with numerous T2 hyperintense, T1 hypointense, and T1-enhancing lesions located in the juxtacortical and periventricular regions, corpus callosum, brainstem, and spinal cord; positive CSF oligoclonal bands; negative serum aquaporin-4 immunoglobulin G (IgG) and myelin oligodendrocyte glycoprotein IgG; and positive serum Epstein-Barr viral capsid antigen IgG.

This case highlights the evaluation indicated for a pediatric patient presenting with a possible demyelinating disorder and the nuances of diagnosing these conditions in prepubertal children particularly. Thoughtful clinical, laboratory, and radiographic investigation is needed for accurate diagnosis to initiate appropriate therapies.

*These authors contributed equally to this work as first authors.

From the Washington University Pediatric MS, Other Demyelinating Disease Center, St. Louis, MO.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Section 1

A 6-year-old neurotypical girl presented with right-sided pain and weakness. Two weeks earlier, she developed right leg pain, dizziness, and difficulty walking. The symptoms fluctuated with some periods of recovery. On the day of admission, she was noted to have a right-sided limp but denied pain. There was no fever, behavioral change, visual symptoms, or bowel/bladder dysfunction. There was no preceding illness, trauma, tick/animal exposure, or travel. Medical history was notable for neonatal encephalopathy status post therapeutic hypothermia without neurologic sequelae. Family history was unremarkable. On neurologic examination, she had a normal mental status. She had pronator drift on the right. Confrontational strength testing was notable for the following: 4/5 strength with right hip flexion and right knee flexion and extension, 2/5 strength with right ankle dorsiflexion, and 4/5 strength with right ankle plantarflexion (per the Medical Research Council scale); strength was 5/5 in all other extremities. Deep tendon reflexes were 3 + on the right. She had 2–3 beats of clonus at the right ankle, and plantar response on the right was extensor. She had mild dysmetria with finger-nose-finger and heel-knee-shin on the right. Her gait was abnormal with circumduction of the right lower extremity. There was no afferent pupillary defect, and limited fundus examination was normal. Eye movements were full, and there was no nystagmus. Her sensory examination was normal. Rectal tone was normal.

Questions for Consideration:

1. What are the potential localizations for her presentation?
2. What are the possible differential diagnoses?

GO TO SECTION 2

Section 2

The patient in this vignette presented with dizziness, right-sided upper and lower extremity weakness, hyperreflexia, and dysmetria. Weakness associated with hyperreflexia and extensor plantar response indicates an upper motor neuron pathology. The pattern of unilateral weakness suggests a lesion of the cortex or the corticospinal tract. Involvement of both the upper and lower extremities suggests a lesion at or above the cervical spinal cord. The finding of dysmetria indicates cerebellar involvement. A complaint of dizziness may be secondary to (1) global impairment of cerebral perfusion (i.e., lightheadedness), (2) dysfunction of the peripheral vestibular system (i.e., peripheral vertigo), or (3) dysfunction of the central vestibular system, which includes the vestibular nuclei, brainstem, and cerebellum (i.e., central vertigo). Overall, the patient's findings indicate a multifocal CNS disorder, such as one involving the left hemispheric corticospinal tract and the pontocerebellar pathways. Alternatively, a focal brainstem lesion involving the right corticospinal tract and pontocerebellar pathways could be implicated.

The differential for this presentation is broad. Demyelinating disorders, including acute disseminated encephalomyelitis (ADEM), multiple sclerosis (MS), myelin oligodendrocyte glycoprotein (MOG) antibody–associated disease (MOGAD), and aquaporin-4 positive neuromyelitis optica spectrum disorder (AQP4-NMOSD), often present with multifocal CNS involvement. A neoplasm, such as a primary brainstem tumor, is also a consideration. Although rare, inflammatory processes that may involve both the brain and spinal cord include CNS vasculitis and CNS-isolated hemophagocytic lymphohistiocytosis (HLH). Infectious causes of CNS dysfunction include viral meningoencephalitis (herpes viruses, arboviruses, human T-lymphocytic virus, and HIV), bacterial meningitis (including tuberculosis meningitis), cerebral abscess, Lyme, Toxoplasmosis, and Bartonella. Parainfectious, paraneoplastic, vascular, and genetic (e.g., leukodystrophies) etiologies should be considered. Of note, although the patient has a history of neonatal encephalopathy, a chronic structural abnormality is unlikely to explain her subacute presentation.

Question for Consideration:

1. What investigations can help narrow the differential diagnosis?

GO TO SECTION 3

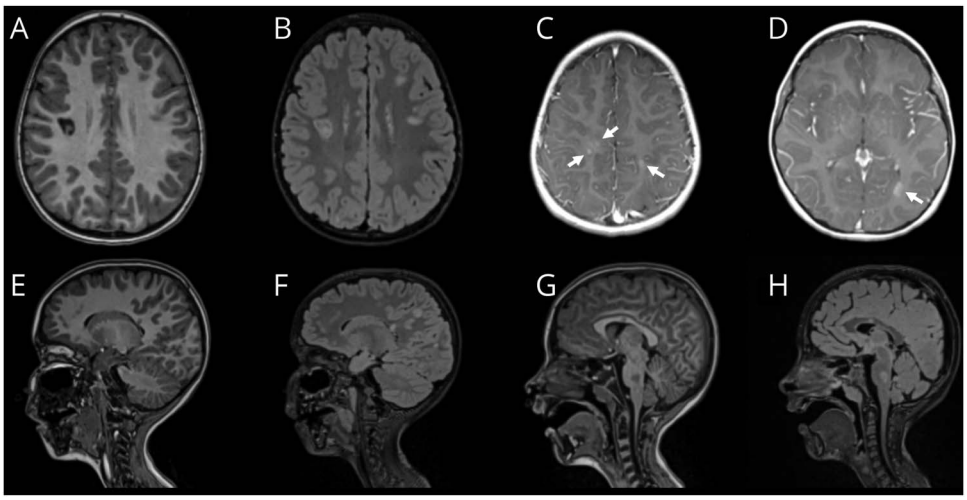
Section 3

An MRI brain with and without contrast demonstrated numerous scattered T2 hyperintense and T1 hypointense lesions involving the subcortical regions, corpus callosum, juxtacortical, periventricular white matter, and right hemi-pons (Figure 1, A, B, E–H). Most lesions were small. The largest lesion was in the right frontal centrum semiovale/corona radiata. Several lesions had faint, ill-defined contrast enhancement (Figure 1C and D). An MRI total spine with and without contrast demonstrated subtle patchy T2 short-tau inversion recovery hyperintense signal abnormality from C2-C6 and at T10 (Figure 2) with no associated enhancement.

Questions for Consideration:

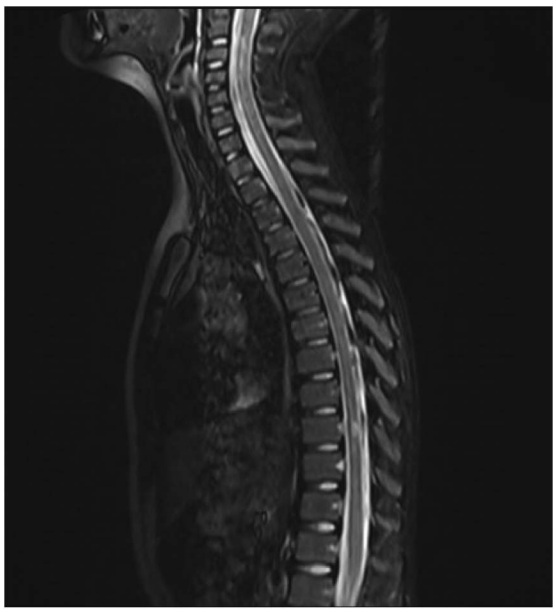
1. What are the possible differential diagnoses based on the imaging?
2. What additional testing is needed to establish a diagnosis?

Figure 1 MRI Images of the Brain



Axial images demonstrating multiple (A) T1-weighted sequence hypointense and (B) fluid-attenuated inversion recovery (FLAIR) sequence hyperintense juxtacortical lesions. (C, D) T1-weighted post-contrast sequences demonstrate several faint, ill-defined contrast-enhancing lesions, most notably in the left peritrigonal white matter. Arrows highlight subtle regions of contrast enhancement. Additional periventricular, subcortical, corpus callosal, and pontine lesions are seen on (E, G) sagittal T1-weighted sequence and (F, H) sagittal FLAIR sequence.

Figure 2 MRI of the Spinal Cord



T2 short tau-inversion recovery (STIR) sequence demonstrating patchy hyperintensity from C2-C6 and a hyperintense lesion at T10

GO TO SECTION 4

Section 4

T2 hyperintense/T1 hypointense lesions involving the corpus callosum, pons, and spinal cord are highly suspicious for a demyelinating process, such as clinically isolated syndrome (CIS), MS, ADEM, AQP4-NMOSD, and MOGAD. Alternative, but less likely diagnostic, considerations include CNS vasculopathy/vasculitis, CNS HLH, or infection.

These imaging findings were particularly concerning for MS or MOGAD. AQP4-NMOSD was less likely, given the absence of optic neuritis or an area postrema syndrome.[1] The lesions were atypical for ADEM, which is often characterized by large, poorly defined lesions of the same chronicity. In addition, her clinical presentation was inconsistent with ADEM, given the absence of impaired consciousness/encephalopathy (a required diagnostic criterion for ADEM in children)[2] and the lack of a prodromal viral illness. The lack of diffusion restriction made CNS vasculitis unlikely. The absence of microhemorrhages on susceptibility-weighted imaging made CNS HLH unlikely.[3] CNS infection such as meningitis was unlikely, given the lack of fever and/or neck stiffness.

A lumbar puncture was performed. CSF studies were notable for a mild pleocytosis (12 nucleated cells, 96% lymphocytes) and 4 unique CSF oligoclonal bands. CSF glucose and protein were normal. CSF culture and gram stain were negative/no growth. CSF flow and cytology were unremarkable. Immunoglobulin G (IgG) index and synthesis rate were normal. CSF paraneoplastic autoantibody evaluation was negative. Serum AQP4-IgG and MOG-IgG were both negative. Triglycerides were mildly elevated; however, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ferritin, and lactate dehydrogenase were all normal. Epstein-Barr virus viral capsid antigen-IgG was positive.

The patient was ultimately diagnosed with pediatric-onset MS (POMS) based on (1) her clinical presentation, (2) the appearance and location of brain and spinal cord lesions, (3) the presence of unique CSF oligoclonal bands, and (3) the reasonable exclusion of alternative diagnoses including MOGAD and AQP4-NMOSD. She was acutely treated with a 5-day course of high-dose intravenous steroids and was then started on fingolimod.

Questions for Consideration:

1. What are the diagnostic criteria for POMS? How well do they apply to prepubertal children?
2. How does POMS differ from adult-onset MS?
3. Which disease-modifying therapies (DMTs) may be used in POMS?

Discussion

Acquired demyelinating syndromes (ADS) of childhood encompass a number of monophasic and relapsing inflammatory conditions of the CNS. These include CIS (e.g., transverse myelitis and optic neuritis), ADEM, MS, NMOSD, and MOGAD. Fifteen to 46 percentage of individuals with pediatric ADS will be diagnosed with MS within 5 years of their initial demyelinating event.[4] Female sex and older age at first presentation have been associated with a higher risk for future MS diagnosis.[5] Epstein-Barr virus positivity has also been strongly associated with POMS.[6] Overall, POMS represents 2%–10% of all MS cases.[4,7] The global incidence of POMS is estimated to be 0.87 (95% CI 0.35–1.40) per 100,000 children and adolescents annually[8] and increases with age (most notably after age 12 years).[9] The onset of MS before 10 years of age is quite rare[5,9] and represents 20%–30% of all cases with POMS.[5]

The diagnosis of POMS, as with adult-onset MS, relies on the objective demonstration of dissemination of CNS demyelination in space and time and the exclusion of alternative diagnoses. This requires a detailed history and physical examination and an MRI of the brain and spinal cord with and without contrast. An MRI of the orbits may be obtained if concerned for optic neuritis. Typical MRI findings consistent with POMS include well-defined ovoid/round lesions with asymmetric distribution involving the periventricular, juxtacortical/cortical, infratentorial, and spinal cord white matter. Young children may, however, have larger, less-well demarcated lesions than those seen in older individuals. Additional evaluation with lumbar puncture (for CSF oligoclonal bands) and visual evoked potentials may be necessary if there is insufficient clinical and MRI data to secure the diagnosis. Further testing, including serum autoantibodies (MOG-IgG and AQP4-IgG) and rheumatologic screening laboratory tests (CRP, ESR, antinuclear antibody, and double-stranded DNA antibody), should be obtained for patients with features atypical of MS. While the 2017 McDonald criteria for MS are highly sensitive and specific for the diagnosis of POMS, caution is needed in patients younger than 11 years, given the lower disease incidence in that age group.[10] In addition, the criteria should not be applied for children with an initial ADEM phenotype; a subsequent attack characteristic of MS is necessary for the diagnosis.[10]

The initial disease course of POMS is relapsing-remitting in more than 98% of patients, compared with 80% of the general MS population.[9,11,12] Compared with their adult counterparts, children and adolescents with MS have higher annualized relapse rates,[13] greater MRI disease burden,[14] and despite having slower disease progression, reach disability landmarks at a younger age.[11] Treatment options for POMS include most of the injectable DMTs used in adult-onset MS (e.g., interferon β-1a and glatiramer acetate) and intermediate or high-efficacy DMTs including dimethyl fumarate, rituximab, natalizumab, and fingolimod—the first Food and Drug Administration-approved treatment for children aged 10 years or older with MS.[15] Timely diagnosis and prompt initiation of DMTs, preferably those of high efficacy, in POMS is critical to reduce relapse risk and limit disability accumulation.

Study Funding

The authors report no targeted funding.

Disclosure

C.M. Gaudioso is a recipient of the National Multiple Sclerosis Society Sylvia Lawry Physician Fellowship award; R. Zolno, A. Wagner, and S. Mar report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* April 12, 2022. Accepted in final form September 13, 2022. Submitted and externally peer reviewed. The handling editor was Whitley Aamodt, MD, MPH.

Appendix Authors

Name	Location	Contribution
Cristina M Gaudioso, MD	Washington University Pediatric MS and other Demyelinating Disease Center, St. Louis, MO	Drafting/revision of the article for content, including medical writing for content
Rachel Zolno, MD	Washington University Pediatric MS and other Demyelinating Disease Center, St. Louis, MO	Drafting/revision of the article for content, including medical writing for content
Anne Wagner, RN	Washington University Pediatric MS and other Demyelinating Disease Center, St. Louis, MO	Drafting/revision of the article for content, including medical writing for content; Additional contributions: contributed to clinical care, Soe Mar
Soe Mar, MD	Washington University Pediatric MS and other Demyelinating Disease Center, St. Louis, MO	Drafting/revision of the article for content, including medical writing for content; additional contributions: contributed to clinical care, Anne Wagner

References

1. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology* 2015;85(2):177-189. doi: 10.1212/wnl.0000000000001729
2. Krupp LB, Tardieu M, Amato MP, et al. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions. *Mult Scler.* 2013;19(10):1261-1267. doi: 10.1177/1352458513484547
3. Benson LA, Li H, Henderson LA, et al. Pediatric CNS-isolated hemophagocytic lymphohistiocytosis. *Neurol Neuroimmunol Neuroinflamm* 2019;6(3):e560. doi: 10.1212/nxi.0000000000000560
4. Waldman A, Ghezzi A, Bar-Or A, Mikaeloff Y, Tardieu M, Banwell B. Multiple sclerosis in children: an update on clinical diagnosis, therapeutic strategies, and research. *Lancet Neurol.* 2014;13(9):936-948. doi: 10.1016/s1474-4422(14)70093-6
5. Chitnis T. Role of puberty in multiple sclerosis risk and course. *Clin Immunol.* 2013;149(2):192-200. doi: 10.1016/j.clim.2013.03.014
6. Nourbakhsh B, Rutatangwa A, Waltz M, et al. Heterogeneity in association of remote herpesvirus infections and pediatric MS. *Ann Clin Transl Neurol.* 2018;5(10):1222-1228. doi: 10.1002/acn3.636
7. Renoux C, Vukusic S, Confavreux C. The natural history of multiple sclerosis with childhood onset. *Clin Neurol Neurosurg.* 2008;110(9):897-904. doi: 10.1016/j.clineuro.2008.04.009
8. Yan K, Balijepalli C, Desai K, Gullapalli L, Druyts E. Epidemiology of pediatric multiple sclerosis: a systematic literature review and meta-analysis. *Mult Scler Relat Disord.* 2020;44:102260. doi: 10.1016/j.msard.2020.102260
9. Jeong A, Oleske DM, Holman J. Epidemiology of pediatric-onset multiple sclerosis: a systematic review of the literature. *J Child Neurol.* 2019;34(12):705-712. doi: 10.1177/0883073819845827
10. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol.* 2018;17(2):162-173. doi: 10.1016/s1474-4422(17)30470-2
11. Renoux C, Vukusic S, Mikaeloff Y, et al. Natural history of multiple sclerosis with childhood onset. *N Engl J Med.* 2007;356(25):2603-2613. doi: 10.1056/nejmoa067597
12. Chitnis T, Glanz B, Jaffin S, Healy B. Demographics of pediatric-onset multiple sclerosis in an MS center population from the Northeastern United States. *Mult Scler.* 2009;15(5):627-631. doi: 10.1177/1352458508101933
13. Benson LA, Healy BC, Gorman MP, et al. Elevated relapse rates in pediatric compared to adult MS persist for at least 6 years. *Mult Scler Relat Disord.* 2014;3(2):186-193. doi: 10.1016/j.msard.2013.06.004
14. Yeh EA, Weinstock-Guttman B, Ramanathan M, et al. Magnetic resonance imaging characteristics of children and adults with paediatric-onset multiple sclerosis. *Brain* 2009;132(12):3392-3400. doi: 10.1093/brain/awp278
15. Chitnis T, Arnold DL, Banwell B, et al. Trial of fingolimod versus interferon beta-1a in pediatric multiple sclerosis. *N Engl J Med.* 2018;379(11):1017-1027. doi: 10.1056/nejmoa1800149

Disputes & Debates: Rapid Online Correspondence

The editors encourage comments on recent articles through Disputes & Debates:

Access an article at *Neurology.org/N* and click on "MAKE COMMENT" beneath the article header.

Before submitting a comment to Disputes & Debates, remember the following:

- Disputes & Debates is restricted to comments about articles published in *Neurology* within 6 months of issue date, but the editors will consider a longer time period for submission if they consider the letter a significant addition to the literature
- Read previously posted comments; redundant comments will not be posted
- Your submission must be 200 words or less and have a maximum of 5 references; the first reference must be the article on which you are commenting
- You can include a maximum of 5 authors (including yourself)

Clinical Reasoning: A 6-Year-Old Girl With Right-Sided Pain and Weakness

Cristina M. Gaudioso, Rachel Zolno, Anne Wagner, et al.

Neurology 2023;100;97-102 Published Online before print October 18, 2022
DOI 10.1212/WNL.0000000000201481