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Thunderclap headache as a first manifestation of acute disseminated encephalomyelitis: case report and literature review

Abdulhamid Çiçek[1,2†], Louise De Temmerman[1*†], Mieke De Weweire[1], Hilde De Backer[1], Maarten Buyle[1] and Frederik Clement[1]

Abstract

Background Acute Disseminated Encephalomyelitis (ADEM) is an acute demyelinating disorder of the central nervous system, characterize by multiple white matter hyperintensities on T2 MRI. Patients usually present with subacute progressive encephalopathy and polyfocal neurological deficits. Possible treatments are corticosteroids, immunoglobulins and plasma exchange. Full clinical recovery is seen in more than half of the cases.

Case We describe a case of a 62-year-old patient presenting with thunderclap headache as the first symptom, two weeks after an upper respiratory tract infection. The clinical course was complicated by progressive coma and intracranial hypertension mandating external ventricular drainage and sedation. Initial treatment with methylprednisolone was unsuccessful but clinical resolution and radiological regression was achieved after plasma exchanges and cyclophosphamide.

Conclusion To our knowledge, this is the first reported case of ADEM presenting with thunderclap headache. Intracranial hypertension with the need for invasive neuromonitoring and pressure management is also a very rare complication of ADEM. In this report, we describe the findings of the literature review concerning ADEM, thunderclap headache and intracranial hypertension.

Keywords Acute disseminated Encephalomyelitis (ADEM), Thunderclap headache, Intracranial hypertension, Secondary headache

Background: acute disseminated encephalomyelitis (ADEM)

Acute Disseminated Encephalomyelitis (ADEM) is an acute immune-mediated polyfocal demyelinating disorder of the central nervous system. It may occur at any age but is most common during childhood and occurs in 67% of the cases after an infection or vaccination [1–4]. Patients usually present with (sub)acute onset of encephalopathy in combination with polyfocal neurologic deficits. Seizures, fever, gradual headache, meningeal signs and vomiting may occur [2–5]. The clinical course is rapidly progressive with maximization of deficits in a couple

†A. Çiçek and L. De Temmerman contributed equally to this work.

*Correspondence:
Louise De Temmerman
louisedetemmerman@gmail.com
[1]Department of Neurology, Delta General Hospital, Roeselare, Belgium
[2]Department of Neurosurgery, Delta General Hospital, Roeselare, Belgium

of days [1]. Pathophysiology is not fully understood but the proposed mechanism is T- cell-mediated cross-activation and response against myelin proteins through a mechanism of molecular mimicry [2–4]. Since there is no distinct biological marker, the diagnosis is based on historical, clinical and radiological features. MRI with T2 and Fluid Attenuated Inversion Recovery (FLAIR) sequences can reveal multiple large and poorly demarcated lesions predominantly in the white matter [2–4]. The differential diagnosis includes multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD), infectious meningoencephalitis, central nervous system vasculitis or malignancy [4]. Cerebrospinal fluid (CSF) analysis is mainly used for exclusion of other infectious diseases, as the possible findings (i.e. pleocytosis with lymphocyte domination and protein elevation) are nonspecific as well [4]. Pathological hallmarks are congestion and swelling with perivenous sleeves of demyelination at a uniform stage (in contrast to MS) and perivascular inflammation [6]. High-dose intravenous corticosteroids followed by prolonged oral tapering over 4–6 weeks is administered as an acute treatment. Alternative options are intravenous immunoglobulins (IVIG) and plasma exchange [4]. Full recovery is seen in 50–75% of cases [3, 4, 7] but mortality rate reaches 6.1% in adults [1].

Thunderclap headache (TCH) as a first clinical manifestation of ADEM has not been described before. Significant intracranial hypertension in ADEM is rarely reported as well. We present a case which combines both and form a hypothesis regarding the pathophysiology.

Case report

A 62-year-old woman admitted to the emergency department with a holocranial thunderclap headache and a subjective binocular vertical diplopia existing for more than 24 h. There was no meningeal irritation or photophobia. She reported having a persisting bronchitis for 16 days and was on a second course of amoxicillin/clavulanic acid, prescribed by her general practitioner. There was no history of travelling or recent vaccinations and she never had fever. Neurological examination was normal with no ophtalmoparesis. Computed tomography (CT), CT angiography (CTA) of the brain and blood analysis were unremarkable. Lumbar puncture showed an opening pressure of 15mmHg/20cmH_2O. Analysis of the cerebrospinal fluid (CSF) revealed increased cellularity with a white blood cell count of 330/ul (with segment 88%, lymphocytes 10% and monocytes 2%), a protein count of 81 mg/dl, glucose level of 62 mg/dl and was negative for intrathecal oligoclonal bands or xanthochromia. Cultures were negative for bacteria and fungi, Polymerase Chain Reaction (PCR) was negative for bacteria (E.Coli, H. Influenzae, L. onocytogenes, N. Meningitidis, S. Agalactiae, S. Pneumoniae) and viruses (Cytomegalovirus, Enterovirus, Herpes simplex virus 1 and 2, Humane herpesvirus 6, Humane parechovirus, Varizella Zoster virus). A masked bacterial meningitis, under a second course of antibiotics, was suspected and the patient was hospitalized with IV ceftriaxone 2 g once a day, Acyclovir 750 mg three times a day and Ampicillin 2 g IV every four hours. The next morning, the patient acutely deteriorated to a subcomatose state with a Glasgow Coma Scale of 11 (eye:3, motor:6, verbal:2) without lateralizing motor or sensory signs. Urgent magnetic resonance imaging (MRI) of the brain showed significant bilateral supra- and infratentorial diffuse white matter hyperintensities on T2 and FLAIR with beginning associated edema (Fig. 1). The periaqueductal grey (PAG) and trigeminal nuclei were affected due to the inflammation. Acute Disseminated Encephalomyelitis (ADEM) was suggested considering the preceding upper respiratory tract infection. Broad infectious serology (including interferon-gamma release assay, human immunodeficiency virus, Borrelia, varicella zoster, Epstein–Barr virus, herpes simplex type 1/2, cytomegalovirus, syphilis, cryptococcus, West Nile and Toxoplasmosis) and neuroinflammatory analysis, including myelin oligodendrocyte glycoprotein (MOG) antibodies and anti-aquaporin 4 (AQP4) antibodies, antibodies for

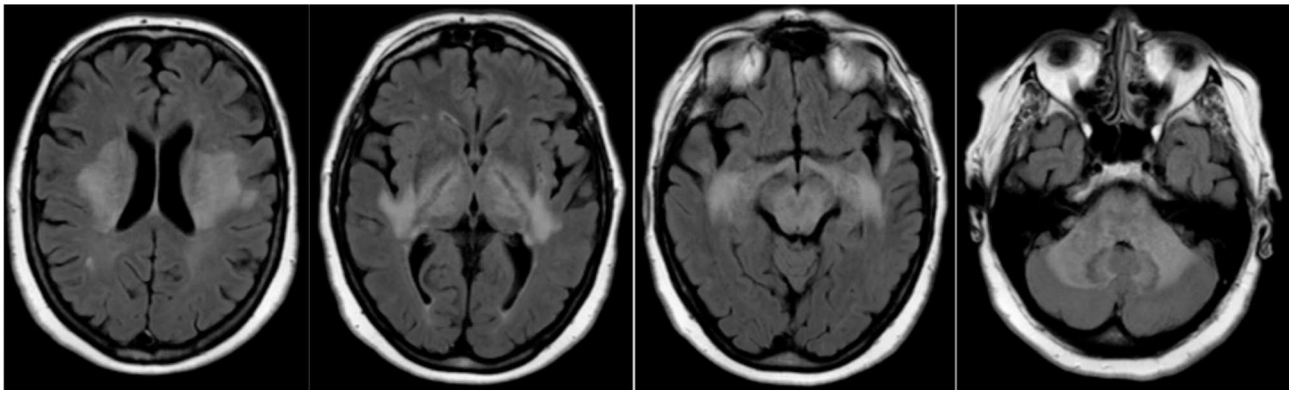

Fig. 1 MRI (T2 FLAIR) showing diffuse white matter hyperintensities with diffuse edema

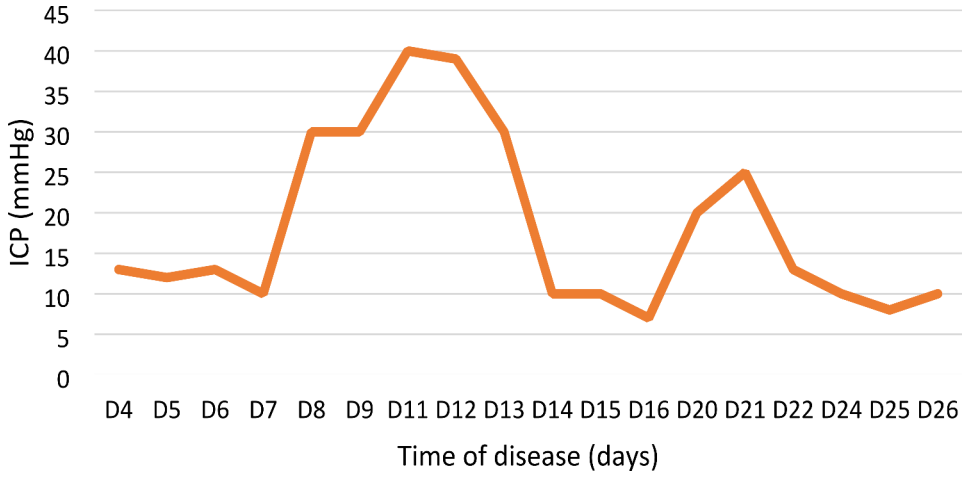

Fig. 2 Graphical overview of ICP spikes on the ICU

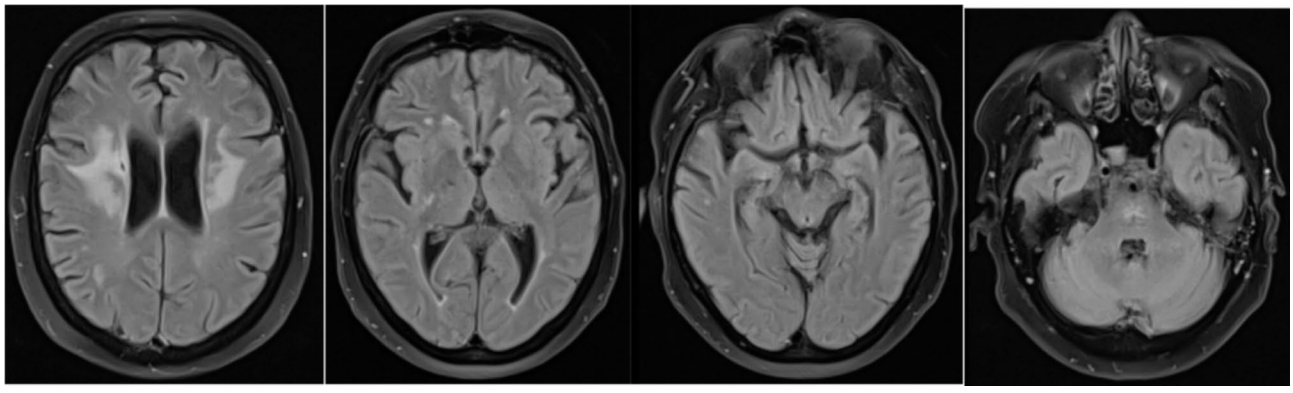

Fig. 3 MRI (T2/FLAIR) after 3.5 months showing progressive resolution

autoimmune encephalitis and paraneoplastic syndromes in serum and CSF were negative. Repeated CSF cytology and flow cytometry could not show malignant cells. Rheumatological and nutritional screening were negative. infections () were negative. A 18-FDG-PET-CT full body did not demonstrate any inflammatory or neoplastic lesions.

High dose IV methylprednisolone (1000 mg/d) was initiated. Regardless, on day 2 of the treatment, the patient had further deteriorated to a comatose state (EMV 2-4-2) with equal and reactive pupils. Obstructive breathing with respiratory failure was evident, with need for intubation and mechanical ventilation. An urgent control CT scan showed progressive white matter abnormalities and edema compressing the basal cisterns and fourth ventricle. Intracranial hypertension was suspected and an external ventricular drain (EVD) was placed for invasive neuromonitoring and CSF drainage. Despite continuous sedation and classical measures such as 30 degrees elevation of the head and hypertonic saline, the ICP was above 20 mmHg for significant periods (Fig. 2). Additional curarisation and sedation was necessary for the following first weeks due to ICP spikes above 30 mmHg.

After 7 days of high dose corticosteroids (five days methylprednisolone 1000 mg/d followed by 125 mg/d) there was a lack of clinical and radiological response and persisting elevated ICP. Therefore, second line treatment with cyclophosphamide and alternate day plasma exchange (PLEX) were simultaneously initiated. After six sessions of PLEX, ICP stabilization with reduced need for sedation and a slow neurological recuperation was achieved. Follow-up imaging showed progressive decrease in T2/FLAIR white matter hyperintensities supra- and infratentorial. Four and a half months after presentation, the patient could leave the hospital with complete neurological recuperation. There was no relapse after six months of clinical and radiological follow-up (Fig. 3). Repeated analysis of anti-MOG and-AQP4 antibodies in serum remained negative.

Literature search

The literature search was carried out on PubMed (Table 1) and restricted to studies published in English. There was no limit on publication date for referencing articles about association between ADEM, intracranial hypertension or thunderclap headache, or headache in other demyelinating diseases/multiple sclerosis (MS).

All the available ADEM articles were screened for items related to increased intracranial pressure, opening pressure or neurosurgery in the title (search 1). The same was applied for more specific searches concerning demyelinating diseases (searches 2 and 3). No articles focusing on TCH and ADEM (search 4) were found. A further search was performed (search 4) focusing on articles about TCH and screening for anything related to ADEM or demyelination in the text. A total of 122 articles concerning TCH were found, from which 85 articles were selected after screening the abstract. An analysis of the selected literature, including > 30 reviews, was performed to search for causes of TCH, with focus on ADEM or demyelinating disorders. The same was applied for demyelinating diseases and headache (searches 5–8).

Discussion

Increased intracranial pressure (ICP) or intracranial hypertension in ADEM

Increased ICP is a complication of a variety of central nervous system pathologies, most commonly space-occupying lesions and inflammation. It is defined as a cerebrospinal fluid (CSF) pressure higher than 20 cm H_2O or 15mmHg (8). In ADEM, intracranial hypertension has been sporadically described both in adults and children, with only a minimal amount of documented articles [9–20]. Since the presenting signs and symptoms of ADEM such as headache, vomiting and encephalopathy are also the main manifestations of intracranial hypertension, these are no useful clinical tools for distinguishing between ADEM with or without increased ICP [10]. ADEM with intracranial hypertension is significantly associated with increased morbidity, prolonged hospitalization, ICU admission, edema and/or herniation requiring neurosurgical management [9]. A retrospective cohort study showed increased cerebrospinal fluid opening pressure in 42% of pediatric patients with ADEM [10]. While none of these patients needed additional measures or pressure management, it suggests that intracranial hypertension is more common in ADEM than documented. Limited data is available about intracranial hypertension in other demyelinating diseases [12, 21]. Comparable ICP's between variable demyelinating diseases and idiopathic intracranial hypertension in children has been described [12]. A few reports associate intracranial hypertension with multiple sclerosis (MS), while others claim the opposite [22–26]. There are some theories for the raised ICP in ADEM or demyelinating diseases. The extensive encephalomyelitis or demyelinating lesions can cause diffuse vasogenic edema [24]. The changes in the CSF composition (increased cytokines, immunoglobulins and leukocytes) can alter the CSF flow dynamics and increase the oncotic pressure. Combined with the edema, this might prevent adequate CSF reabsorption at arachnoid villi and cause hydrocephalus [12, 21, 24].

In very rare cases, ADEM can lead to significant ICP rises requiring decompressive neurosurgery with favorable outcomes on mortality [14–16, 18–20]. Functional outcome has yet to be shown in prospective studies.

In our case, the intracranial hypertension was probably due to diffuse inflammation and edema, peaking 7–15 days after onset. There was no hydrocephalus. Imaging correlated accurately to the clinical state of the patient, further supporting this theory (Fig. 4).

Thunderclap headache (TCH) and ADEM

TCH is defined by the International Classification of Headache Disorders (ICHD-3) as a sudden severe headache reaching maximum intensity within one minute and lasting for more than five minutes [27]. Next to primary thunderclap headache, it is associated with a nonlimited series of intracranial disorders: subarachnoid hemorrhage, reversible cerebral vasoconstrictive syndrome, cervical artery dissection, venous thrombosis, unruptured aneurysm, posterior reversible encephalopathy

Table 1 Search overview

Search number	Search (Filter: English)	Results	Selected
1	Acute Disseminated Encephalomyelitis [Title] OR ADEM [Title] → Titles screened for anything related to intracranial pressure, opening pressure or neurosurgery	171	14
2	(demyelination [title] OR demyelinating [title]) and (intracranial [title] or pressure [title])	23	2
3	(multiple sclerosis [title] OR MS [title]) AND (intracranial [title] OR CSF [title] or cerebrospinal fluid [title]) AND (pressure [title] or hypertension [title])	6	5
4	Headache [title] and (sudden [title] or acute [title] or thunderclap [title]	122	85
5	(Acute Disseminated Encephalomyelitis [Title] OR ADEM [Title]) AND headache [title]	0	0
6	Demyelination [Title] AND headache [title]	0	0
7	Demyelinating [Title] AND headache [title]	2	1
8	(Multiple Sclerosis [Title] OR MS [Title]) AND headache [title]	43	36

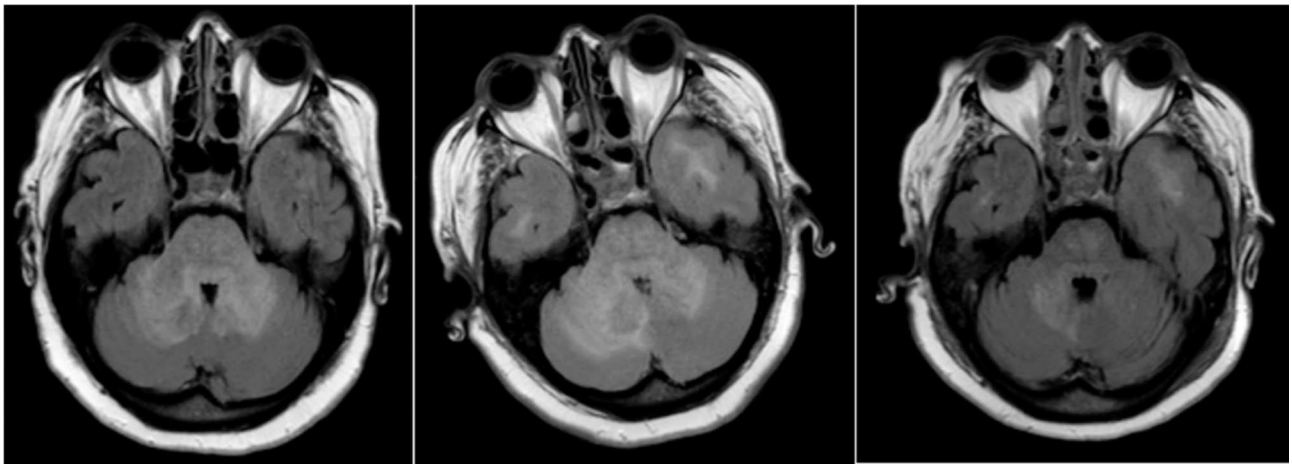

Fig. 4 Consequent MRI scans 3, 10 and 17 days after onset

syndrome, hypertensive encephalopathy, spontaneous intracranial hypotension, ischemic and hemorrhagic stroke, intracranial mass lesions, meningoencephalitis, vasculitis (giant cell arteritis), pituitary apoplexy, acute glaucoma, carbon monoxide poisoning, colloid cyst, acute sinusitis and even myocardial infarction [28–112]. Neither ADEM nor demyelination has been reported as a differential diagnosis.

In an effort to explain the TCH as the presenting manifestation of ADEM, a search for headache in demyelinating diseases was conducted. A significantly increased prevalence of trigeminal neuralgia in MS patients is reported with lifetime prevalence ranging from 4.0 to 9.5%, in comparison to 0.16–0.3% in the general population. Demyelinating lesions of the trigeminal nucleus or tracti in the brainstem are considered as causative [113, 114]. Cluster headache and glossopharyngeal neuralgia have been sporadically reported as well, again with brainstem lesions as presumed mechanisms [113, 115–118]. The prevalence of other headache syndromes in MS has been reviewed multiple times, showing highly variable numbers between 4.0 and 78%, with migraine and tension-type headache (TTH) being the most common [113, 114, 119–133]. Migraine was found to be more frequent in relapsing-remitting MS (RR-MS) and TTH more prevalent in progressive MS [134]. Further elaboration has been described in RR-MS, with more stabbing headache during a relapse and more a migraine type headache or TTH during remission [119, 135, 136]. Although without a clear causative correlation, headache as the first clinical manifestation of cerebral MS has been reported as well [126, 137, 138]. It is important to mention that there are case-control studies that could not show a difference in 1 year prevalence of migraine and TTH between MS and normal population [139, 140].

One theory of headache in demyelinating disorders suggests that the inflammation is not limited to the white matter, but also extends to the gyri and meninges [113, 126, 128, 135]. Demyelination in the pain-producing centers in the midbrain is another explanation where a plaque in the PAG has shown to be associated with a higher risk of developing migraine [113, 129, 134, 141–143]. Another significant part of headache in MS is iatrogenic due to side effects of medication such as interferons, natalizumab and fingolimod. Medication overuse headache is also reported [113, 119, 120, 127, 131, 132, 144]. In our case, we have no radiological evidence for hydrocephalus or mass effect at the initial presentation, excluding these as explanation for TCH as the initial presentation. Hereby, brain edema only developed three days after the TCH, making meningeal reaction or pressure on vasculature with stimulation of nociceptors also less probable. We assume excessive demyelinating inflammation in the brainstem anatomically both impacting the PAG and the trigeminal nuclei as a plausible explanation.

Conclusion

TCH as a first clinical manifestation of ADEM has not been described before. Significant intracranial hypertension in ADEM is rarely reported as well. We present a case which combines both, which seem to be caused by excessive demyelinating inflammation. The delayed intracranial hypertension was probably due to diffuse inflammation leading to edema. We assume the presentation with TCH was due to acute inflammation of the periaqueductal grey and trigeminal nuclei. The patient made a significant recovery after corticosteroids, plasma exchange, cyclophosphamide and cerebrospinal fluid drainage. In this report, we review the correlation of TCH and intracranial hypertension in ADEM.

Key findings

- ADEM should be in differential diagnosis of patients presenting with thunderclap headache.
- Acute inflammation in the brainstem anatomically both impacting the PAG and the trigeminal nuclei as a plausible explanation for thunderclap headache in a demyelinating disorder.

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Author contributions
Abdulhamid Çiçek conceived the presented manuscript. Abdulhamid Çiçek and Louise De Temmerman did the literature review and wrote the manuscript. The total contribution of Abdulhamid Çiçek and Louise De Temmerman was equal. Frederik Clement and Maarten Buyle reviewed the article with comments. Mieke De Weweire and Hilde De Backer reviewed the article and had no additional comments.

Data availability
The authors have no unpublished data to report.

Declarations

Ethical approval and consent to participate
Written and signed consent to publish the information was obtained from the patient.

Consent for publication
Written and signed consent to publish the information was obtained from the patient.

Consent to publish
Written and signed consent to publish the information was obtained from the patient.

Conflict of interests
The authors have no conflict to report.

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References

1. Koelman DLH, Mateen FJ. Acute disseminated encephalomyelitis: current controversies in diagnosis and outcome. J Neurol. 2015;262(9):2013–24.
2. Sáenz-Farret M, Cansino-Torres MA, Sandoval-Rodríguez V, Navarro-Ibarra R, Zúñiga-Ramírez C. The spectrum of Acute disseminated encephalomyelitis and mild encephalopathy with reversible Splenial Lesion. Case Rep Neurol Med. 2019.
3. Taghdiri MM, Amouzadeh MH, Esmail Nejad SS, Abasi E, Alipour A, Akhavan Sepahi M. Epidemiological, clinical, and laboratory characteristics of acute disseminated encephalomyelitis in children: a retrospective study. Iran J Child Neurol. 2019.
4. Cole J, Evans E, Mwangi M, Mar S. Acute Disseminated Encephalomyelitis in Children: An Updated Review Based on Current Diagnostic Criteria. Pediatric Neurology. 2019.
5. Pohl D, Alper G, Van Haren K, Kornberg AJ, Lucchinetti CF, Tenembaum S, et al. Acute disseminated encephalomyelitis: updates on an inflammatory CNS syndrome. Neurology. 2016;87(9 Suppl 2):S38–45.
6. Esposito S, Di Pietro GM, Madini B, Mastrolia MV, Rigante D. A spectrum of inflammation and demyelination in acute disseminated encephalomyelitis (ADEM) of children. Autoimmun Rev. 2015;14(10):923–9.
7. Kaunzner UW, Salamon E, Pentsova E, Rosenblum M, Karimi S, Nealon N, et al. An Acute disseminated Encephalomyelitis-Like Illness in the Elderly: neuroimaging and neuropathology findings. J Neuroimaging. 2017;27(3):306–11.
8. Thurtell MJ. Idiopathic Intracranial Hypertension. CONTINUUM Lifelong Learning in Neurology. 2019.
9. Narayan RN, Wang C, Greenberg BM. Acute Disseminated Encephalomyelitis (ADEM) and Increased Intracranial Pressure Associated With Anti–Myelin Oligodendrocyte Glycoprotein Antibodies. Pediatr Neurol. 2019.
10. Orbach R, Schneebaum Sender N, Lubetzky R, Fattal-Valevski A. Increased intracranial pressure in Acute disseminated Encephalomyelitis. J Child Neurol. 2019.
11. Garcia-Merino A, Garcia-Sola R, Vela L, Martin-Gonzalez E. Intracranial pressure monitoring in acute disseminated encephalomyelitis in childhood. Crit Care Med. 1990.
12. Morgan-Followell B, Aylward SC. Comparison of Cerebrospinal Fluid opening pressure in children with demyelinating disease to children with primary intracranial hypertension. J Child Neurol. 2017.
13. Miyamoto K, Kozu S, Arakawa A, Tsuboi T, Hirao JI, Ono K et al. Therapeutic hypothermia with the use of intracranial pressure monitoring for acute disseminated encephalomyelitis with brainstem lesion: a case report. In: J Child Neurol. 2014.
14. Granget E, Milh M, Pech-Gourg G, Paut O, Girard N, Lena G et al. Life-saving decompressive craniectomy for acute disseminated encephalomyelitis in a child: a case report. Child's Nerv Syst. 2012.
15. Dombrowski KE, Mehta AI, Turner DA, McDonagh DL. Life-saving hemicraniectomy for fulminant acute disseminated encephalomyelitis. Br J Neurosurg. 2011.
16. Ahmed AI, Eynon CA, Kinton L, Nicoll JAR, Belli A. Decompressive craniectomy for acute disseminated encephalomyelitis. Neurocrit Care. 2010.
17. Vanlandingham M, Hanigan W, Vedanarayanan V, Fratkin J. An uncommon illness with a rare presentation: neurosurgical management of ADEM with tumefactive demyelination in children. Child's Nerv Syst. 2010.
18. Sekula RF, Marchan EM, Baghai P, Jannetta PJ, Quigley MR. Central brain herniation secondary to fulminant acute disseminated encephalomyelitis: implications for neurosurgical management: Case report. J Neurosurg. 2006.
19. Refai D, Lee MC, Goldenberg FD, Frank JI. Decompressive hemicraniectomy for acute disseminated encephalomyelitis: Case report. Neurosurgery. 2005.
20. Von Stuckrad-Barre S, Klippel E, Foerch C, Lang JM, Du Mesnil, de Rochemont R, Sitzer M. Hemicraniectomy as a successful treatment of mass effect in acute disseminated encephalomyelitis. Neurology. 2003.
21. Narula S, Liu GT, Avery RA, Banwell B, Waldman AT. Elevated cerebrospinal fluid opening pressure in a pediatric demyelinating disease cohort. Pediatr Neurol. 2015.
22. Bateman GA, Lechner-Scott J, Copping R, Moeskops C, Yap SL. Comparison of the sagittal sinus cross-sectional area between patients with multiple sclerosis, hydrocephalus, intracranial hypertension and spontaneous intracranial hypotension: a surrogate marker of venous transmural pressure? Fluids Barriers CNS. 2017.
23. Meyer-Schwickerath R, Haug C, Hacker A, Fink F, Seidel D, Hartung HP et al. Intracranial venous pressure is normal in patients with multiple sclerosis. Mult Scler J. 2011.
24. Williams BJ, Skinner HJ, Maria BL. Increased intracranial pressure in a case of pediatric multiple sclerosis. J Child Neurol. 2008.
25. Newman NJ, Selzer KA, Bell RA. Association of Multiple Sclerosis and Intracranial Hypertension. J Neuro-Ophthalmology [Internet]. 1994;14(4):189???192. http://journals.lww.com/00041327-199412000-00001
26. David P, Uncini A, Scoppetta C. Intracranial hypertension syndrome as initial symptom of late onset multiple sclerosis. A case report. Acta Neurol (Napoli). 1983.
27. Olesen J, Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. Cephalalgia [Internet]. 2018;38(1):1–211. http://journals.sagepub.com/doi/10.1177/0333102417738202
28. Bahra A. Other primary headaches—thunderclap-, cough-, exertional-, and sexual headache. J Neurol. 2020.
29. Baraness L, Baker AM. Acute Headache. Treasure Island. FL); 2020.
30. Raffaelli B, Neeb L, Israel-Willner H, Körner J, Liman T, Reuter U et al. Brain imaging in pregnant women with acute headache. J Neurol. 2018.
31. Finocchi C. Acute headache during pregnancy. Neurol Sci. 2018.
32. Vgontzas A, Robbins MS. A Hospital Based Retrospective Study of Acute Postpartum Headache. Headache. 2018.

33. Raffaelli B, Siebert E, Körner J, Liman T, Reuter U, Neeb L. Characteristics and diagnoses of acute headache in pregnant women – a retrospective cross-sectional study. J Headache Pain. 2017.
34. Alons IME, Goudsmit BFJ, Jellema K, van Walderveen MAA, Wermer MJH, Algra A. Yield of computed tomography (CT) angiography in patients with Acute Headache, normal neurological examination, and normal non contrast CT: a Meta-analysis. J Stroke Cerebrovasc Dis. 2018.
35. Gulati D, William M, Ray J. Sudden onset headache in a 50 year old woman. BMJ (Online; 2017.
36. Lomazow S. The Headache That Changed History: The Most Famous Thunderclap Headache. Headache. 2017.
37. Budweg J, Sprenger T, De Vere-Tyndall A, Hagenkord A, Stippich C, Berger CT. Factors associated with significant MRI findings in medical walk-in patients with acute headache. Swiss Med Wkly. 2017.
38. Qin C, Pan C, Tian DS. Clinical reasoning: sudden-onset pulsatile headache in a previously healthy young man. Neurology. 2017.
39. Zhang J, Anil G. Thunderclap headache in a patient with depression: question. J Clin Neurosci. 2017.
40. Sjulstad AS, Alstadhaug KB. What is Currently the Best Investigational Approach to the Patient With Sudden-Onset Severe Headache? Headache. 2019.
41. Zhang J, Anil G. Thunderclap headache in a patient with depression: answer. J Clin Neurosci. 2017.
42. Ravishankar K. Looking at thunderclap headache differently? Circa 2016. Ann Indian Acad Neurol. 2016.
43. Kalani MYS, Spetzler RF. Woman with sudden-onset headache. Annals of Emergency Medicine; 2016.
44. Grangeon L, Ozel G, Guégan-Massardier E, Lefaucheur R. Bath-related thunderclap headache: Case report of a male patient. Headache. 2016.
45. Chu KH, Howell TE, Keijzers G, Furyk JS, Eley RM, Kinnear FB et al. Acute Headache presentations to the Emergency Department: a Statewide cross-sectional study. Acad Emerg Med. 2017.
46. Akhter M, Chen SP. Vascular emergencies and Shared decision-making in patients with Thunderclap Headache. Academic Emergency Medicine; 2016.
47. Malhotra A, Wu X, Forman HP. Response to Vascular emergencies and Shared decision making in patients with Thunderclap Headache. Acad Emerg Med. 2016.
48. Robbins MS, Farmakidis C, Dayal AK, Lipton RB. Acute headache diagnosis in pregnant women: a hospital-based study. Neurology. 2015.
49. Schwedt TJ. Thunderclap headache. CONTINUUM Lifelong Learning in Neurology. 2015.
50. Cooper JG, Smith B, Hassan TB. A retrospective review of sudden onset severe headache and subarachnoid haemorrhage on the clinical decision unit: looking for a needle in a haystack? Eur J Emerg Med. 2016.
51. Guryildirim M, Kontzialis M, Ozen M, Kocak M. Acute headache in the emergency setting. Radiographics. 2019.
52. Devenney E, Neale H, Forbes RB. A systematic review of causes of sudden and severe headache (Thunderclap Headache): should lists be evidence based? J Headache Pain. 2014.
53. Glover RL, Vollbracht S, Robbins MS. Acute postpartum headache. Headache. 2014.
54. Aladakatti R, Sannakki LB, Cai PY, Derequito R. Thunderclap headache: it is always sub-arachnoid hemorrhage. Is it? - a Case report and review. Surg Neurol Int. 2014.
55. Forbes RB. Acute Headache. Ulster Medical Journal. 2014.
56. Dilli E. Thunderclap headache. Current Neurology and Neuroscience Reports. 2014.
57. Norbedo S, Naviglio S, Murru FM, Cavallin R, Giurici N, Rabusin M et al. A boy with sudden headache. Pediatr Emerg Care. 2014.
58. Conlin S, Fenning SJ, Weir G, Raza Z, Phelps RG, Gifford FJ. Sudden, severe headache: an unexpected culprit. Lancet. 2014.
59. Hainer BL, Matheson EM. Approach to acute headache in adults. Am Fam Physician. 2013.
60. Leyon JJ, Gupta T, Srinivasan V, Senthil L. A thunderclap headache. J Clin Neurosci. 2013.
61. Chróinín DN, Lambert J. Sudden headache, third nerve palsy and visual deficit: thinking outside the subarachnoid haemorrhage box. Age Ageing. 2013.
62. Umar M, Carius B. What is causing this patient's sudden headache? J Am Acad Physician Assistants. 2019.
63. Ducros A, Bousser MG. Thunderclap headache. BMJ (Online). 2013.
64. Mortimer AM, Bradley MD, Stoodley NG, Renowden SA. Thunderclap headache: diagnostic considerations and neuroimaging features. Clin Radiol. 2013.
65. Simoni P, Meunier B, Deprez M, Racaru T, Martin D. A 36-year-old man with sudden severe headache. Skeletal Radiol. 2011.
66. Simoni P, Meunier B, Deprez M, Racaru T, Martin D. 36-year-old man with sudden severe headache. Skeletal Radiol. 2011.
67. Ferrante E, Tassorelli C, Rossi P, Lisotto C, Nappi G. Focus on the management of thunderclap headache: from nosography to treatment. J Headache Pain. 2011.
68. Nahas SJ. Diagnosis of acute headache. Curr Pain Headache Rep. 2011.
69. Coutinho JM, Stam J. A rare cause of thunderclap headache. BMJ. 2011.
70. Linn FHH. Primary thunderclap headache. Handbook of Clinical Neurology. 2010.
71. Zarkou S, Dilli E, Dodick DW. 55-year-old man with thunderclap headache. Mayo Clin Proc. 2010.
72. Bø SH, Davidsen EM, Benth JŠ, Gulbrandsen P, Dietrichs E. Cerebrospinal fluid opening pressure measurements in acute headache patients and in patients with either chronic or no pain. Acta Neurol Scand. 2010.
73. Long D, Koyfman A, Long B. The Thunderclap Headache: Approach and Management in the Emergency Department. J Emerg Med. 2019.
74. Hewett R, Counsell C. Documentation of cerebrospinal fluid opening pressure and other important aspects of lumbar puncture in acute headache. Int J Clin Pract. 2010.
75. Kuo CL, Chiu YH, Chen JD, How CK, Lam C. Thunderclap headache: images from headache. Headache. 2010.
76. Mistry N, Mathew L, Parry A. Thunderclap headache. Pract Neurol. 2009.
77. Levin M. Teaching case presentation - primary thunderclap headache. Headache. 2009.
78. Sharma P, Poppe AY, Eesa M, Steffenhagen N, Goyal M. Postpartum thunderclap headache. Can Med Assoc J. 2008.
79. Breen DP, Duncan CW, Pope AE, Gray AJ, Al-Shahi Salman R. Emergency department evaluation of sudden, severe headache. QJM. 2008.
80. Savitz SI, Edlow J. Thunderclap headache with normal CT and lumbar puncture: further investigations are unnecessary: for. Stroke. 2008.
81. Moussouttas M, Mayer SA. Thunderclap headache with normal CT and lumbar puncture: further investigations are unnecessary: against. Stroke. 2008.
82. Davis SM, Donnan GA. Thunderclap headache: CT and lumbar puncture but occasionally more! Stroke. 2008.
83. Wang SJ, Fuh JL, Wu ZA, Chen SP, Lirng JF. Bath-related thunderclap headache: a study of 21 consecutive patients. Cephalalgia. 2008.
84. Yang CW, Fuh JL. Thunderclap headache: an update. Expert Review of Neurotherapeutics; 2018.
85. Price L, Parghi C, Khan R. Thunderclap headache-and a tender neck. Lancet. 2007.
86. Schwedt TJ. Clinical spectrum of thunderclap headache. Expert Rev Neurother. 2007.
87. Matharu MS, Schwedt TJ, Dodick DW. Thunderclap headache: an approach to a neurologic emergency. Current Neurology and Neuroscience Reports; 2007.
88. Friedman BW, Hochberg ML, Esses D, Grosberg B, Corbo J, Toosi B et al. Applying the International classification of Headache disorders to the Emergency Department: an Assessment of Reproducibility and the frequency with which a unique diagnosis can be assigned to every Acute Headache Presentation. Ann Emerg Med. 2007.
89. Schwedt TJ, Matharu MS, Dodick DW. Thunderclap headache. Lancet Neurol. 2006.
90. Gladstone JP, Dodick DW, Evans R. The young woman with postpartum thunderclap headache. Headache. 2005.
91. Peters G, Nahser HC, Shaw MDM, Smith DF. Bleeding thunderclap headache. Hosp Med. 2004.
92. Farhan M, Hutt J. Diagnosing acute headache. Clin Med (Northfield Il). 2004.
93. Davenport R. Diagnosing acute headache. Clinical Medicine. J R Coll Physicians Lond. 2004.
94. Spierings ELH. Acute, subacute, and chronic headache. Otolaryngologic Clinics of North America; 2003.
95. Chinthapalli K, Logan AM, Raj R, Nirmalananthan N. Assessment of acute headache in adults - what the general physician needs to know. Clin Med J R Coll Physicians Lond. 2018.
96. Webb S, Bone I, Lindsay K. The investigation of acute severe headache suggestive of probable subarachnoid haemorrhage: a hospital-based study. Br J Neurosurg. 2003.
97. Linn FHH, Wijdicks EFM. Causes and management of thunderclap headache: a comprehensive review. Neurologist. 2002.

98. Levin M. The acute severe headache - Assessment and treatment. Compr Ther. 2002.
99. Dodick DW, Eross EJ. A not so uncommon cause of thunderclap headache. Headache. 2002.
100. Davenport R. Acute headache in the emergency department. J Neurol Neurosurg Psychiatry. 2002;72(2):ii33–7.
101. Dodick DW. Thunderclap headache. J Neurol Neurosurg Psychiatry. 2002.
102. Dodick DW. Thunderclap headache. Current pain and headache reports. 2002.
103. Dodick DW. Thunderclap headache. Headache. 2002.
104. Jacome DE. Transitional interpersonality thunderclap headache. Headache. 2001.
105. Lewis DW, Qureshi F. Acute headache in children and adolescents presenting to the emergency department. Headache. 2000.
106. Malhotra A, Wu X, Gandhi D, Sanelli P. The patient with Thunderclap Headache. Neuroimaging Clinics of North America; 2018.
107. Diamond ML. Emergency department management of the acute headache. Clin Cornerstone. 1999.
108. Stevenson RJ, Dutta D, MacWalter RS. The management of acute headache in adults in an acute admissions unit. Scott Med J. 1998.
109. Markus HS. A prospective follow up of thunderclap headache mimicking subarachnoid haemorrhage. J Neurol Neurosurg Psychiatry [Internet]. 1991;54(12):1117–8. http://jnnp.bmj.com/cgi/doi/https://doi.org/10.1136/jnnp.54.12.1117
110. Clarke CE, Shepherd DI, Chishti K, Victoratos G, Pearce JMS, THUNDERCLAP HEADACHE. Lancet [Internet]. 1988;332(8611):625. https://linkinghub.elsevier.com/retrieve/pii/S0140673688906575
111. Olesen J, Aebelholt A, Veilis B. The Copenhagen Acute Headache Clinic: Organization, Patient Material and Treatment results. Headache J Head Face Pain. 1979.
112. Grossman S, Rothstein A, Conway J, Gurin L, Galetta S. Clinical reasoning: a 41-year-old man with thunderclap headache. Neurology. 2018.
113. Husain F, Pardo G, Rabadi M. Headache and its management in patients with multiple sclerosis. Current Treatment Options in Neurology; 2018.
114. Putzki N, Pfriem A, Limmroth V, Yaldizli Ö, Tettenborn B, Diener HC et al. Prevalence of migraine, tension-type headache and trigeminal neuralgia in multiple sclerosis. Eur J Neurol. 2009.
115. Pelikan JB, McCombe JA, Kotylak T, Becker WJ. Cluster Headache as the Index Event in MS: A Case Report. Headache. 2016.
116. Mijajlovic M, Aleksic V, Covickovic-Sternic N. Cluster headache as a first manifestation of multiple sclerosis: case report and literature review. Neuropsychiatr Dis Treat [Internet]. 2014;2269. http://www.dovepress.com/cluster-headache-as-a-first-manifestation-of-multiple-sclerosis-case-r-peer-reviewed-article-NDT
117. Leandri M, Cruccu G, Gottlieb A. Cluster headache-like pain in multiple sclerosis. Cephalalgia. 1999.
118. Gentile S, Ferrero M, Vaula G, Rainero I, Pinessi L. Cluster headache attacks and multiple sclerosis. J Headache Pain. 2007.
119. Togha M, Abbasi Khoshsirat N, Moghadasi AN, Mousavinia F, Mozafari M, Neishaboury M et al. Headache in relapse and remission phases of multiple sclerosis: a case-control study. Iran J Neurol. 2016.
120. Villani V, Prosperini L, Ciuffoli A, Pizzolato R, Salvetti M, Pozzilli C et al. Primary headache and multiple sclerosis: preliminary results of a prospective study. Neurol Sci. 2008.
121. Boneschi FM, Colombo B, Annovazzi P, Martinelli V, Bernasconi L, Solaro C et al. Lifetime and actual prevalence of pain and headache in multiple sclerosis. Mult Scler. 2008.
122. Alstadhaug K, Breivik K, Rusic Z. Recurrent headache due to MS plaque. Headache. 2008;48(3):453–4.
123. Vacca G, Marano E, Brescia Morra V, Lanzillo R, De Vito M, Parente E et al. Multiple sclerosis and headache co-morbidity. A case-control study. Neurol Sci. 2007.
124. Freedman MS, Gray TA. Vascular headache: a presenting symptom of multiple sclerosis. Can J Neurol Sci / J Can des Sci Neurol. 1989.
125. Headache in multiple sclerosis. Br Med J. 1969;2(5659):713–4.
126. Gebhardt M, Kropp P, Hoffmann F, Zettl UK. Headache at the time of first symptom manifestation of multiple sclerosis: a prospective, longitudinal study. Eur Neurol. 2019.
127. Beckmann Y, Türe S. Headache characteristics in multiple sclerosis. Mult Scler Relat Disord. 2019.
128. Gebhardt M, Kropp P, Jürgens TP, Hoffmann F, Zettl UK. Headache in the first manifestation of multiple sclerosis – prospective, multicenter study. Brain Behav. 2017.
129. Tabby D, Majeed MH, Youngman B, Wilcox J. Headache in Multiple Sclerosis. Int J MS Care [Internet]. 2013;15(2):73–80. https://doi.org/10.7224/1537-2073.2012-035
130. Applebee A. The Clinical Overlap of Multiple Sclerosis and Headache. Headache J Head Face Pain [Internet]. 2012;52:111–6. http://doi.wiley.com/https://doi.org/10.1111/j.1526-4610.2012.02243.x
131. Kister I, Caminero AB, Herbert J, Lipton RB. Tension-type Headache and Migraine in Multiple Sclerosis. Curr Pain Headache Rep [Internet]. 2010;14(6):441–8. http://link.springer.com/https://doi.org/10.1007/s11916-010-0143-5
132. Putzki N, Katsarava Z. Headache in multiple sclerosis. Current Pain and Headache Reports; 2010.
133. Nicoletti A, Patti F, Fermo S, Lo, Liberto A, Castiglione A, Laisa P et al. Headache and Multiple Sclerosis: A Population-Based Case-Control Study in Catania, Sicily. Cephalalgia [Internet]. 2008;28(11):1163–9. http://journals.sagepub.com/doi/https://doi.org/10.1111/j.1468-2982.2008.01662.x
134. La Mantia L, Prone V. Headache in multiple sclerosis and autoimmune disorders. Neurol Sci. 2015.
135. Klein M, Woehrl B, Zeller G, Straube A. Stabbing Headache as a Sign of Relapses in Multiple Sclerosis. Headache J Head Face Pain [Internet]. 2013;53(7):1159–61. https://doi.org/10.1111/head.12138
136. Sandyk R, Awerbuch GI. The Co-Occurrence of Multiple Sclerosis and Migraine Headache: The Serotoninergic Link. Int J Neurosci [Internet]. 1994;76(3–4):249–56. http://www.tandfonline.com/doi/full/10.3109/00207459408986007
137. Mariotti P, Nociti V, Cianfoni A, Stefanini C, De Rose P, Martinelli D et al. Migraine-Like Headache and Status Migrainosus as Attacks of Multiple Sclerosis in a Child. Pediatrics [Internet]. 2010;126(2):e459–64. http://pediatrics.aappublications.org/cgi/doi/https://doi.org/10.1542/peds.2009-2098
138. Cortesi M, Balottin U, Teutonico F, Fusar-Poli P, Veggiotti P. Atypical onset of multiple sclerosis in an adolescent with monosymptomatic chronic tension-type headache. Journal of paediatrics and child health. Volume 45. Australia; 2009. pp. 395–6.
139. Gustavsen M, Celius E, Winsvold B, Moen S, Nygaard G, Berg-Hansen P et al. Migraine and frequent tension-type headache are not associated with multiple sclerosis in a Norwegian case-control study. Mult Scler J – Exp Transl Clin. 2016.
140. Terlizzi R, Merli E, Buccellato E, Giannini G, Favoni V, Pierangeli G et al. P037. Headache in multiple sclerosis: prevalence and clinical features in a case control-study. J Headache Pain. 2015.
141. Gee JR, Chang J, Dublin AB, Vijayan N. The association of brainstem lesions with migraine-like headache: an imaging study of multiple sclerosis. Headache. 2005.
142. Haas DC, Kent PF, Friedman DI. Headache caused by a single lesion of multiple sclerosis in the Periaqueductal Gray Area. Headache J Head Face Pain. 1993.
143. Mariotti P, Nociti V, Stefanini MC, Cianfoni A, Veltri S, Ferrantini G et al. Chronic Migraine-Like Headache Caused by a Demyelinating Lesion in the Brain Stem. Pain Med [Internet]. 2012;13(4):610–2. https://academic.oup.com/painmedicine/article-lookup/doi/https://doi.org/10.1111/j.1526-4637.2012.01344.x
144. Fragoso YD, Adoni T, Gomes S, Goncalves MVM, Matta APDC, Mendes MF et al. Persistent headache in patients with multiple sclerosis starting treatment with fingolimod. Headache. 2015.

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