

# Acute Disseminated Encephalomyelitis (ADEM) After Pneumococcal Meningitis In A Child

**THOMAS FOIADELLI**

Fondazione IRCCS Policlinico San Matteo

**CHIARA TRABATTI** (✉ [chiara.trabatti@gmail.com](mailto:chiara.trabatti@gmail.com))

Fondazione IRCCS Policlinico San Matteo <https://orcid.org/0000-0003-0601-6284>

**FRANCESCO BASSANESE**

Fondazione IRCCS Policlinico San Matteo

**ENRICO LANDI**

Fondazione IRCCS Policlinico San Matteo

**AMELIA LICARI**

Fondazione IRCCS Policlinico San Matteo

**ALESSANDRO ORSINI**

Azienda Ospedaliero Universitaria Pisana

**SABINO LUZZI**

Fondazione IRCCS Policlinico San Matteo

**GIAN LUIGI MARSEGLIA**

Fondazione IRCCS Policlinico San Matteo

**SALVATORE SAVASTA**

Fondazione IRCCS Policlinico San Matteo

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## Case report

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## Abstract

**Background:** Acute disseminated encephalomyelitis (ADEM) is an inflammatory demyelinating disorder of the central nervous system (CNS), whose pathogenesis is still debated. It occurs more frequently in children, and the first neurological symptoms usually appear between 2 and 4 weeks after a trigger event, such as an infection or vaccination. Several viral agents have been related to the development of ADEM, while bacteria and parasites are less frequently involved. Severe *Streptococcus pneumoniae* infection has been rarely described as a trigger for CNS demyelination in particularly predisposed subjects.

**Case presentation:** A 10 year old girl was evaluated for headache, fever and vomit. CSF analysis revealed pleocytosis and presence of *S. pneumoniae* antigen, and proper antibiotic therapy for bacterial meningitis was started, with rapid improvement. A breach in the right frontal bone, due to a car accident occurring the previous year, was considered the gateway for pneumococcal infection. Three days after admission, the girl developed drowsiness, altered speech and left hemiparesis. Brain MRI showed multiple T2-hyperintense bilateral lesions in the supratentorial white matter, and ADEM was diagnosed. Considering the underlying bacterial meningitis, intravenous immunoglobulins were preferred to steroid therapy, and the patient progressively recovered. However, due to recurrence of encephalopathic symptoms after 11 days, high-dose intravenous steroid therapy was performed. The neurological outcome was favourable, with complete regression of the white matter lesions after 4 months and absence of relapses over a follow-up period of 2 years.

**Conclusions:** Occurrence of ADEM following pneumococcal meningitis is rare, and very few cases have been described in children. It should be suspected in case of persistence, recurrence or onset of new symptoms despite adequate antimicrobial treatment, relying on brain MRI for a thorough differential diagnosis. High level of surveillance is mandatory in patients with predisposing factors to invasive pneumococcal disease. In some cases, acute demyelination can occur few days after the onset of meningitis; pathogenetic mechanisms are not yet fully clarified and the choice of the correct therapeutic approach can be challenging.

## Background

Acute disseminated encephalomyelitis (ADEM) is an inflammatory demyelinating disorder of the central nervous system (CNS). It is more frequent in childhood, with average age at onset of 5 to 8 years and slight male predominance (1), even though several cases have also been reported in adults. The clinical course is usually abrupt and monophasic (2, 3). Presenting features can be heterogeneous and include acute or subacute encephalopathy which cannot be explained by fever (i.e. behavioural change, drowsiness or altered consciousness) with polyfocal motor or sensory deficits (4), on the basis of the affected areas of the CNS. Paraparesis, paraesthesia, dysarthria and impaired extrinsic ocular motility can be frequently observed, as well as seizures, ataxia, urinary retention or extrapyramidal signs, being however these features common to other neurological diseases (5). Systemic symptoms, such as fever, headache, fatigue, malaise or nausea can also be associated with ADEM (6). Brainstem involvement can lead to central respiratory failure in up to 11–16% of patients (1).

Magnetic Resonance Imaging (MRI) typically shows ill-defined white matter lesions of the brain and often of the spinal cord; thalami and basal ganglia are also frequently involved (7). Diagnostic criteria for ADEM were firstly proposed by the International Pediatric Multiple Sclerosis Study Group (IPMSSG) in 2007 (8), and revised in 2013 (9), on the basis of clinical and imaging findings. ADEM should be also differentiated from disseminated CNS tumours, which are however characterized by specific molecular and radiological patterns aiding the differential diagnosis in most of the cases (10–14). Nevertheless, lack of specific biological markers still makes ADEM a diagnosis of exclusion. The pathogenesis of ADEM is yet unclear. ADEM is historically considered a post-infectious or post-vaccinal disorder, as the first neurological symptoms usually occur between 2 and 4 weeks after a trigger event, as a recent immunization or a febrile viral illness (64–93% of the cases), typically involving the upper respiratory tract (1, 15–17). Structural similarities between the pathogen and host cells (“molecular mimicry”) or direct infection of the CNS by neurotropic pathogens have been hypothesized as possible mechanisms causing the typical inflammatory reaction surrounding the cerebral blood vessels with perivenular demyelination (1, 18). Viral triggers commonly associated with ADEM include influenza virus, enterovirus, measles, mumps, rubella, varicella-zoster virus, Epstein–Barr virus, cytomegalovirus, hepatitis A and B and coxsackievirus (19, 20). Parasitic infections, such as malaria or toxoplasmosis, have also been recently reported (21, 22). Moreover, several bacterial triggers can occasionally play a role, including *M. Pneumoniae*, *C. Pneumoniae*, *H. Influenzae*, *Salmonella*, *Borrelia burgdorferi*, *Leptospira*, *Legionella*, *Rickettsia*, *Campylobacter* and  $\beta$ -hemolytic *Streptococcus* (19, 23–25). Rarely, also *Streptococcus pneumoniae* infection has associated to ADEM. This pathogen can be responsible for mild infections, as otitis media,

sinusitis or bronchitis, or for more severe and invasive diseases, like pneumonia or meningitis. To date, few cases of ADEM developing after pneumococcal meningitis have been reported in particularly predisposed subjects, mainly adults (19, 26–32), *Table 1*. Risk factors and pathogenetic mechanisms of this disease are still debated.

## Case Presentation

A 10-year-old caucasian girl was brought to our attention due to intermittent fever since one week. The day before, vomit, headache and altered consciousness had appeared. She was previously healthy, with normal growth and development, and absence of chronic morbidities. At a first clinical examination, the patient appeared in poor general conditions and confused. She was febrile (39 °C) and tachycardic (102 bpm), with normal blood pressure and oxygen saturation. Cardio-thoracic and abdominal examination was normal; meningeal signs were negative and neurological examination did not reveal any focal deficits. Blood tests showed high C-reactive protein (CRP 25.5 mg/dl; normal values [NV] < 0.5 mg/dl), high erythrocyte sedimentation rate (ESR 58 mm/h; NV < 15 mm/h) and leukocytosis with high neutrophil count (22,800/ $\mu$ L; NV 1,500-7,000/ $\mu$ L). Chest X-ray and fundus oculi evaluation were normal.

An electroencephalogram (EEG), recorded in the first 24 hours from admission, showed diffuse slowing of the background activity, particularly in the posterior regions (Fig. 1a). A lumbar puncture was subsequently performed; cerebrospinal fluid (CSF) was turbid, with 5,040 white blood cells/ $\text{mm}^3$  (NV < 2/ $\text{mm}^3$ ), hypoglycorrhachia (< 4 mg/dl, NV 50–80 mg/dl) and high total protein content (359 mg/dl, NV 15–45 mg/dl). Gram staining showed numerous polymorphonuclear leucocytes, and the antigen of *S. pneumoniae* antigen was detected, while the search for the most frequent neurotropic viruses with polymerase chain reaction (PCR) was negative. Diagnosis of pneumococcal meningitis was therefore confirmed, and therapy with ceftriaxone (2 g/day), vancomycin (15 mg/kg every 8 hours) and dexamethasone (0.15 mg/kg every 6 hours) was started, with significant clinical and biochemical improvement within 48 hours. Vomit and fever ceased from the second day after admission, headache improved, CRP and total leukocyte count decreased to 1.8 mg/dl and 8,140/ $\mu$ L, respectively.

On the third day after admission, however, the girl developed drowsiness, altered speech and left hemiparesis. She had impaired photomotor reflexes and bilateral patellar hyporeflexia. Auditory brain responses were normal, visual evoked potentials showed delayed cortical response on both sides, and somatosensitive evoked potentials evidenced altered cortical responses after bilateral tibial nerve stimulation. A second EEG showed slower background activity compared to the previous one, with high-amplitude monomorphic delta waves (Fig. 1b). Given the rapid worsening of her neurological conditions, we performed a brain MRI. Multiple bilateral T2-hyperintense lesions were seen in the supratentorial white matter, with moderate diffusion restriction in the left frontal subcortical area and in the right peritrigonal area. No significant contrast enhancement was noticed. On the basis of clinical and imaging data, criteria for diagnosis of ADEM were fulfilled. Furthermore, MRI revealed a bone breach in the posterior wall of the right frontal sinus, representing a possible gateway for pneumococcal invasion (Fig. 2a,b,c). In the light of this clue, past history was newly explored and the parents reported that the child had been involved in a car accident with consequent head trauma, one year before. A CT scan, performed at that time in her country of origin, showed a fracture in the frontal bone, with minimal bilateral sub-arachnoid hemorrhage, fracture of the nasal pyramid and right frontal sinus hematoma. No specific neurological or surgical follow-up was done, nor imaging re-evaluation was performed. Moreover, a thorough review of the vaccination certificates of the child pointed out a lack of immunization against *S. pneumoniae*, *N. meningitidis* type B and C, Measles, Mumps and Rubella.

Intravenous immunoglobulin (IVIG) treatment was started at the dose of 0.4 g/kg/day for 5 days. After an initial improvement, neurological conditions of the patient worsened again on day 11 after admittance (day 8 after the first IVIG administration), with severe headache, altered mental status and lower limb areflexia. CRP and white blood cell count were normal. High-dose intravenous methylprednisolone (30 mg/kg/day) was therefore administered for 5 days, with prompt improvement. After this treatment a new brain MRI was performed, showing partial regression of the previously described lesions (Fig. 2c,d,e), while CSF isoelectrofocusing showed absence of oligoclonal bands. Oral tapering with prednisone was then continued over six weeks, with complete recovery.

A head CT scan, performed for pre-surgical purpose, clearly defined the bone gap (12 × 5 × 4 mm) adjacent to the lateral wall of the right frontal sinus and a little bone breach in the roof of the right orbit (Fig. 3). Three months after the acute event, cranialization of the frontal sinus was performed, without complications. A brain MRI, performed four months after the acute event, showed complete regression of the previously described white matter lesions. Post-surgical oedema in the frontal lobe gradually resolved, leaving a

little subcortical gliotic lesion. Over a follow-up period of 2 years, no demyelinating relapses were recorded. The patient completed her vaccination schedule and underwent a strict neurological follow-up. Neurological examination was completely and stably normalized, as well as somatosensitive and visual evoked potentials. No major cognitive or speech disability was recorded; some learning difficulties were though reported, because of slight mnemonic problems.

## Discussion And Conclusions

Few cases of ADEM developing after bacterial meningitis have been reported so far, and its diagnosis may be difficult. This diagnosis should be suspected in case of lack of clinical improvement, recurrence or onset of new neurological symptoms in patients receiving adequate antibiotic and supportive therapy (33). In some cases, after an initial improvement, patients can develop a sudden and unexplained encephalopathic symptoms (27, 29), as described in our patient. In other cases, patients may show persistence of altered mental status and fever or even severe neurological deterioration, requiring mechanical ventilation (19, 26, 30, 31). In these situations, the criterion of “encephalopathy”, necessary for the clinical suspicion of ADEM, may be difficult to assess, as an altered consciousness can be partly explained by fever or by the underlying CNS infection. Lumbar puncture and brain and spinal cord MRI are fundamental tools for differential diagnosis. MRI scan allows to assess the number, location and extension of the lesions; when performed in the acute phase of ADEM, it typically shows diffuse, poorly demarcated large lesions involving predominantly the cerebral white matter. Deep grey matter lesions in the thalami or basal ganglia can be also present (9, 30, 31). CSF examination is useful to differentiate ADEM from other inflammatory or autoimmune diseases, and to determine the presence of auto-antibodies (e.g. anti-myelin oligodendrocyte glycoprotein, MOG) which can be indicative for recurrence (3, 34–39).

Due to the limited number of cases and diagnostic difficulties, it is unclear if meningoencephalitis progressing to ADEM is a truly rare event or just underreported. Moreover, the causative microorganism can be identified only in a small number of patients, making it difficult to identify risk factors and pathogenetic mechanisms (33, 40, 41). *Streptococcus pneumoniae* has been rarely described, and the development of related demyelinating CNS disease is reported only after serious infections, like meningitis. ADEM is traditionally considered a *post-infectious* disorder, as the time before the onset of neurological symptoms is usually sufficiently long for the development of an adaptive immune response (2–4 weeks). In this case, molecular mimicry between causative pathogens and host cells causes T-cell activation (42). In experimental animal models of autoimmune allergic encephalitis (EAE) induced by *S. pneumoniae*, damage was mediated by toll-like receptor 2 (TLR2), which can specifically recognize teichoic and lipoteichoic acid (LTA), major constituents of the cell wall of this bacterium. Pneumolysin is also an agonist of TLR4. Also tumour necrosis factor-alpha (TNF $\alpha$ ) and interleukin-6 (IL-6) have been indicated as important immunostimulatory mediators, activating leukocytes and microglial cells, and which can enter the brain tissue in regions without a tight blood-brain barrier (43, 44).

In our paediatric patient, such as in other cases reported in the literature (26, 28, 30), the onset of neurological symptoms occurred within a shorter interval (few days). This rather accounts for a *para-infectious* mechanism, as latency is too rapid to allow an autoimmune reaction after a primary exposure to a microorganism. Direct invasion and damage of the CNS by *S. pneumoniae* is supposed in this case, as already described for other pathogens (45). No post-mortem studies are available, though, to support this hypothesis, while brain biopsy was performed only in one patient (26), without identification of any microbial material. Disruption of the blood-brain barrier by the pathogen can allow CNS-confined autoantigens to leak into the systemic circulation, causing breakdown of tolerance and consequent induction of self-reactive T-cell activation (46). This mechanism could explain why the short latency of onset of neurological symptoms usually occurs after severe pneumococcal infection, while milder infections require a longer time to activate an immune response, as described in the EAE murine model (44).

In this light, risk factors for the development of severe *S. pneumoniae* infection have to be considered. In our pediatric case, a bone breach due to a previous trauma was regarded as the gateway for infection, and the lack of an adequate vaccination schedule did not prevent the girl to develop a serious course of the disease. Also post-surgical breaches, inadequately treated upper-airway infections, immunosuppression and splenectomy (26) have been reported in patients who developed ADEM after bacterial meningitis. In the few pediatric cases described, inadequate or absent immunization against *S. pneumoniae* was reported (30, 31). Though ADEM is primarily a pediatric disease (1), vaccination campaigns and the widespread diffusion of pneumococcal immunization in children could be the reasons, in this case, of the lower incidence of neurological complications in this age group. Conversely, even if ADEM can also be considered a post-vaccinal complication, only one case has been described following *S. pneumoniae* vaccination in an adult patient (47). These evidences should further reinforce the need for vaccinations, at all ages.

First-line treatment of ADEM is widely based on intravenous high-dose methylprednisolone, eventually followed by a slow oral tapering with prednisone over 4–6 weeks. IVIG are considered in case of failure, as a second line treatment (48, 49). All reported cases of ADEM following pneumococcal meningitis were treated with pulse doses of steroids for 3–10 days (*Table 1*), which proved to be effective. Another patient, following pneumococcal meningitis, was diagnosed with acute transverse myelitis associated with evidence of widespread white matter brain lesions, which though did not fulfil the diagnostic criteria for ADEM; he was treated with high-dose steroids, with prompt recovery (50). In only one pediatric case steroids and IVIG were administered at the same time (31). The occurrence of demyelination and worsening neurological symptoms few days after a bacterial meningitis, though, may create some uncertainty on the use of high-dose steroids. In our case, IVIG were chosen a first-line therapy to avoid further immunosuppression in a patient whose treatment with antibiotics had just started and with a probable yet inadequate clearance of the bacterial agent from the CNS. Because of re-exacerbation of symptoms at the eleventh day after admission, she was indeed treated with high-dose steroids, with complete recovery. This worsening did not fulfil the criteria for multiphasic ADEM, as it occurred before than three months after the onset (9), but it was considered due to a lack of proper response to the first-line treatment. A similar treatment course was described by Jorens in 2005 in an adult woman (51). In this case, two days after diagnosis of pneumococcal meningitis, patchy areas of increased signal intensity on T2-weighted images were noticed in both white and grey matter, interpreted as focal areas of ischaemia with cytotoxic oedema, secondary to necrotising vasculitis and thrombosis. First-line treatment with IVIG was ineffective, so high-dose corticosteroids were administered. Even though this patient did not properly fulfil ADEM criteria, myelin disruption was thought to be consequent to parenchymal insult and immunomodulatory therapy was therefore effective.

ADEM following pneumococcal meningitis is rare, and differential diagnosis can be challenging, especially in children. Further studies are needed to clarify the pathogenetic mechanisms and to evaluate the proper therapeutic approach, which have to be administered promptly in order to avoid long-term sequelae.

## List Of Abbreviations

ADEM Acute Disseminated Encephalomyelitis

CNS Central Nervous System

CSF Cerebrospinal fluid

CRP C-reactive proteine

EAE Experimental Allergic Encephalomyelitis

EEG Electroencephalogram

IVIG Intravenous immunoglobulin

MRI Magnetic Resonance Imaging

## Declarations

### ***Ethics approval and consent to participate***

The parents signed an informed consent to participate. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

### ***Consent for publication***

The parents signed an informed consent for publication of clinical data.

### ***Availability of data and materials***

The patient data, described in this report, are stored in Policlinico San Matteo network and can be accessible only to authorized staff. Further details will be provided upon request to the Corresponding Author.

### ***Competing interests***

The authors declare that they have no competing interests.

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### ***Authors' contributions***

SS and TF performed the patients' clinical evaluation and decided the diagnostic and therapeutic process. SL reviewed the surgical indications and procedures. FB, EL, CT wrote the first draft of the manuscript and performed a review of the literature; SS and TF reviewed it. AO contributed with substantial intellectual content, and critical revision. All the authors reviewed and approved the final paper.

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### ***Author's information***

Not applicable

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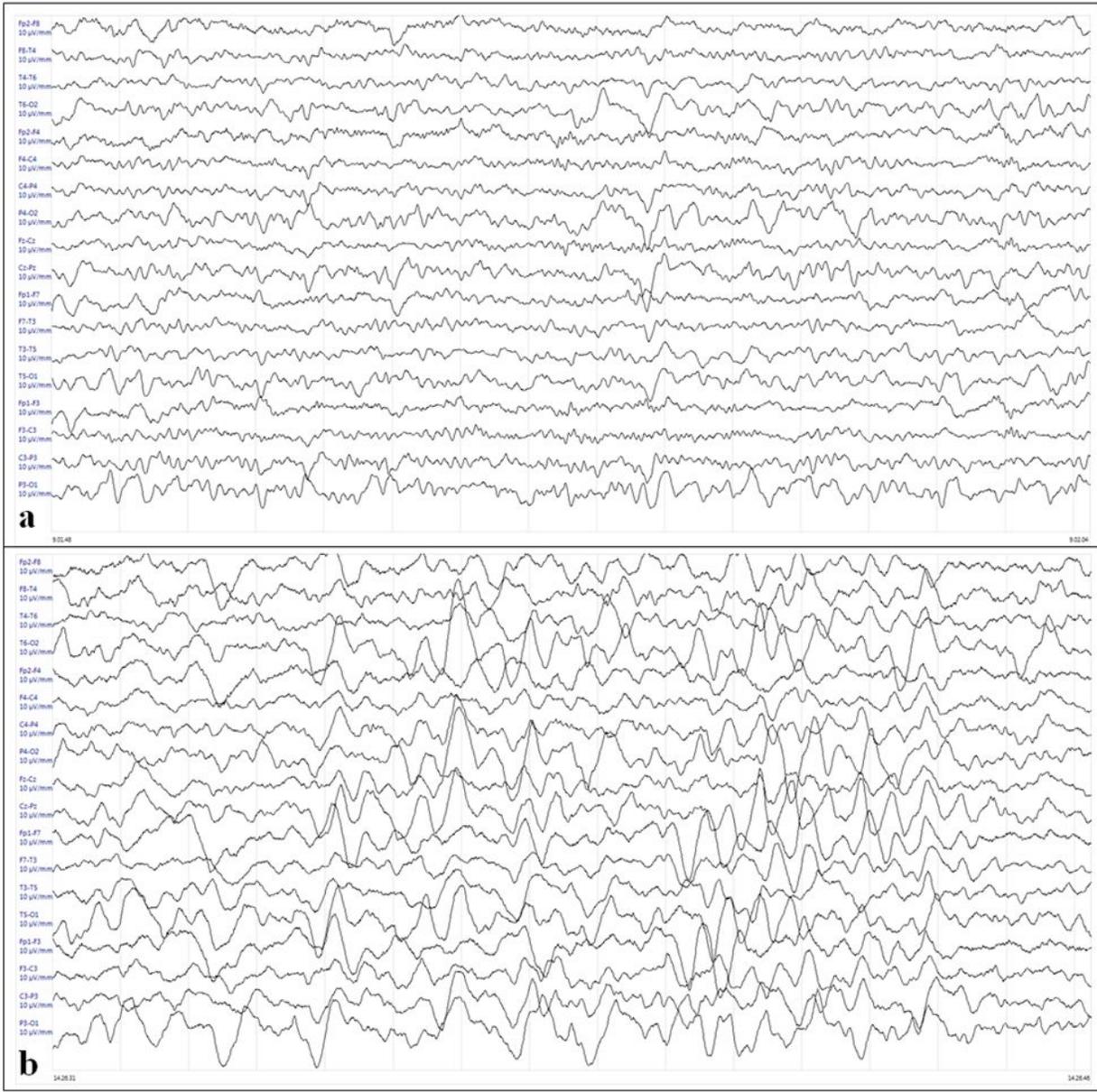
## Table

**Table 1** – List and features of similar cases of ADEM following streptococcal meningitis reported in literature.

		Age/gender	Time of ADEM diagnosis after meningitis	Type and location of brain lesions	Therapy	Risk factors	Outcome
ADULT	<i>Huhn, 2014</i> (19)	61 y, F	2 days	large bilateral white matter lesions	10-day pulse of methylprednisolone	splenectomy without pneumococcal vaccination	recovery, no further relapses
	<i>Majzoobi, 2014</i> (12)	27 y, M	10 days	hyper-signal in T2 images, with symmetric patterns in subcortical, periventricular, and pons regions	prednisolone e.v. for 10 days, followed by oral tapering	-	full recovery within a three-month follow-up
	<i>Ueda, 2009</i> (20)	58 y, M	11 days	tumor-like hyperintensity signal lesions with ring enhancements in the right frontal lobe	corticosteroid pulse therapy for 6 days	-	recovery
	<i>Kureshiro, 2008</i> (22)	57 y, F	13 days	white matter lesions on frontal lobe and temporal lobe seen in T2-weighted images	3-day high-dose methylprednisolone	-	recovery
	<i>Ohnishi, 2007</i> (21)	39 y, M	4 days	high-intensity lesions in the white cerebral matter	3-day high-dose methylprednisolone	-	visual impairment
PEDIATRIC	<i>Jorens, 2008</i> (23)	7 months, F	3 days	multiple areas of increased signal intensity involving both white and gray matter	pulse dose of methylprednisolone for three days	no pneumococcal vaccination	brain atrophy, hearing loss, epilepsy, hypotonus
	<i>Yu, 2013</i> (24)	4 y, F	8 days	multifocal changes mainly in white matter (top of bilateral cerebral ventricles and centrum semiovale), with bithalamic involvement	high-dose intravenous methylprednisolone (20 mg/kg for 5 days) and 2 g/kg IVIG	no pneumococcal vaccination	recovery, no further relapses after 3 y follow-up

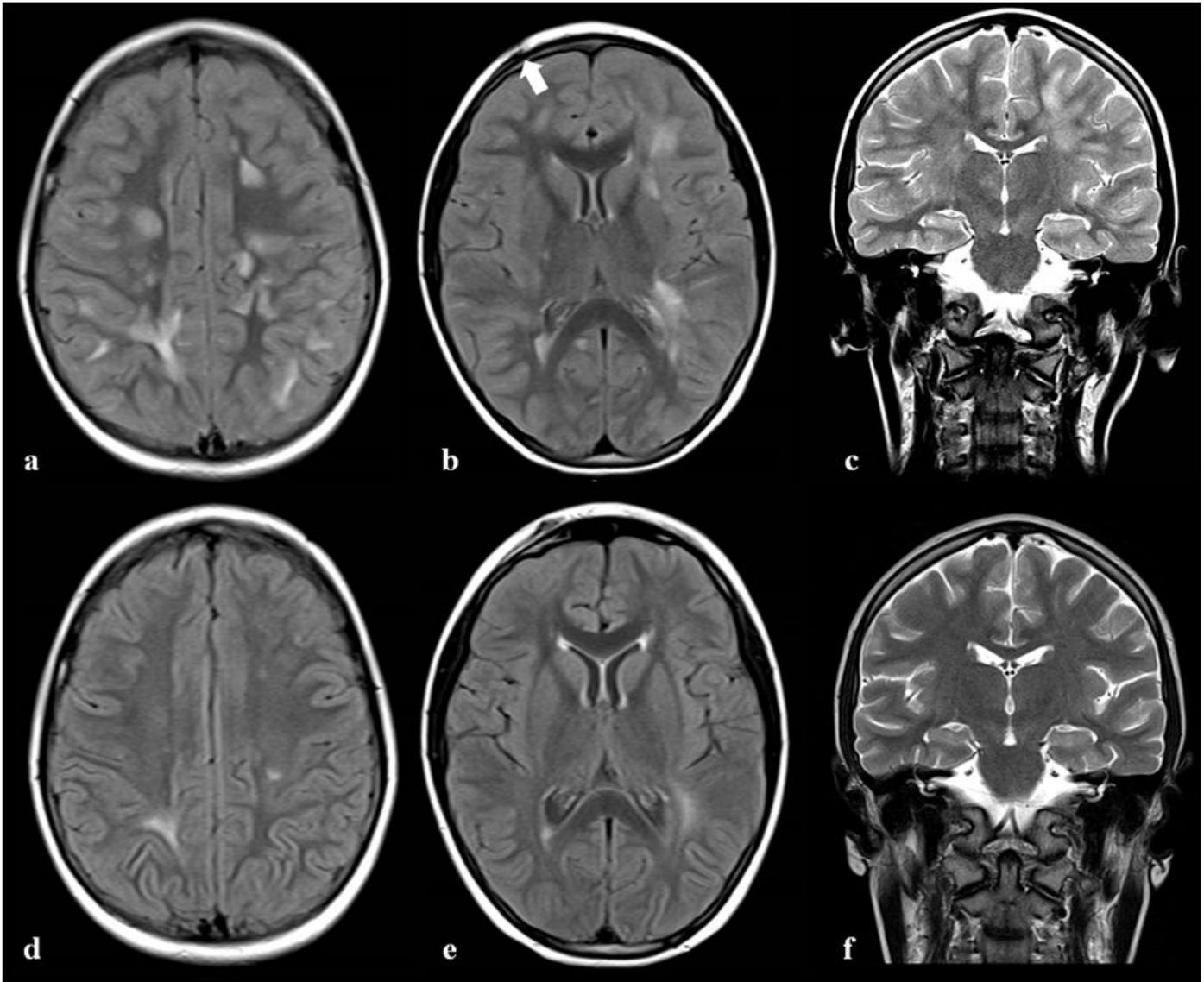
Another case report has been cited in the paper by *Kureshiro et al.*(22), but no abstract is available (Kikuchi K, Takahashi S, Uematsu Dai et al. : *A case of acute disseminated encephalomyelitis caused by pneumococcal meningitis*. Saitama Medical Association Journal 1999; 33: 886-889).

## Figures



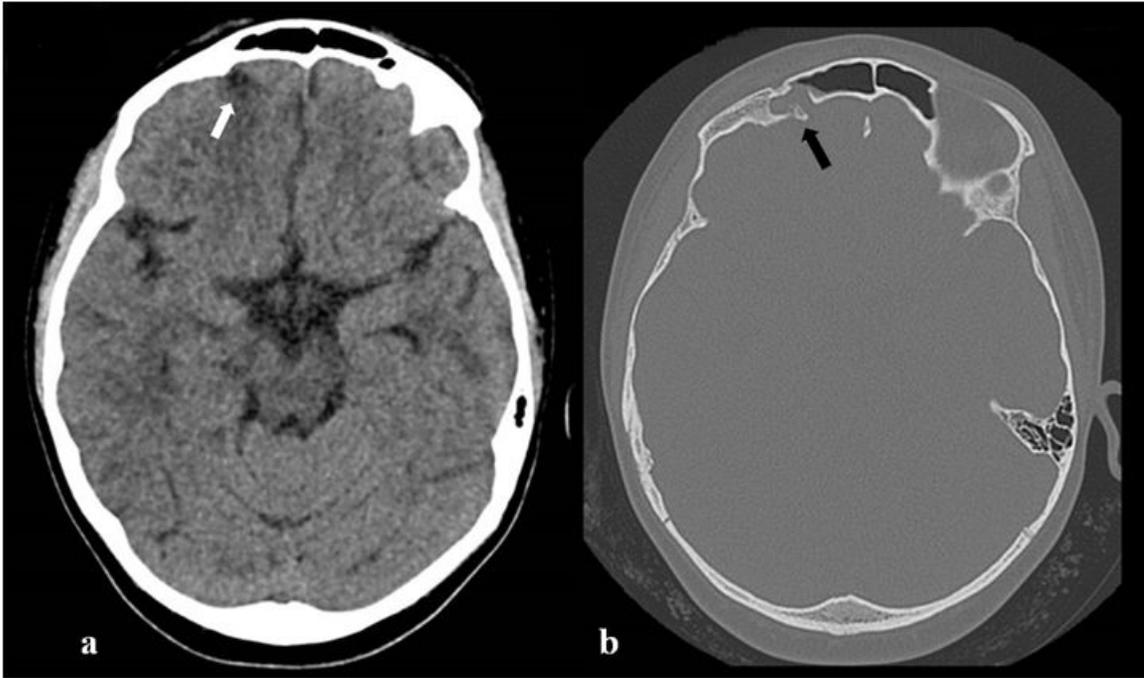
**Figure 1**

EEG traces recorded during day 1 and day 3 after admission [a] EEG performed at admission (diagnosis of pneumococcal meningitis), showing slowing of the background activity, particularly in the posterior regions. [b] EEG performed on the third day after admission (worsening of neurological conditions leading to the diagnosis of ADEM): slow background activity, with high-amplitude diffuse monomorphic delta waves (1-2 Hz).



**Figure 2**

Pre and post-treatment brain MRI in our 10-year-old patient. [a,b,c] Brain MRI performed on day 3 after admission, when neurological conditions of the patient worsened in spite of decreasing of inflammatory parameters and progressive normalization of CSF analysis. Multiple T2-hyperintense bilateral lesions in the supratentorial white matter, with moderate diffusion restriction in the left frontal subcortical area and in the right peritrigonal area, leading to the diagnosis of ADEM. Evidence of bone breach in the posterior wall of the right frontal sinus (white arrow in b). [c,d,e] Brain MRI performed on day 17 after admission, at the end of high-dose steroid therapy. Marked reduction in number and size of the previously described white matter lesions, with persistence of small lesions in the periventricular areas and of point signal alteration in the fronto-parietal subcortical areas.



**Figure 3**

CT scan performed on day 17, aimed at better characterize the bone lesion discovered in the right frontal sinus. Right cortico-subcortical hypodense area in the frontal lobe, compatible with a gliotic-malacic lesion, result of a previous parenchymal post-traumatic insult (white arrow in a). Bone gap (12 x 5 x 4 mm) with sclerotic margins just adjacent to the lateral wall of the right frontal sinus and little bone breach in the roof of the right orbit (black arrow in b). These findings are compatible with a previous bone blown-in traumatism and consequent parenchymal lesion.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [CAREchecklist.pdf](#)