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CASE SERIES

Acute flaccid myelitis and enterovirus infection: a severe emerging disease

Mielitis flácida aguda e infeccion por enterovirus: una enfermedad grave emergente

Raúl Bustos B.[a,g], Franco Díaz[b,c,d], Camila Cores[b], Francisca Castro Z.[f], Pablo Cruces[b,d,e]

[a]Unidad Cuidados Intensivos Pediátricos, Clínica Sanatorio Alemán. Concepción Chile.
[b]Unidad de Paciente Critico Pediátrico, Hospital El Carmen de Maipú. Santiago, Chile.
[c]Escuela de Medicina, Universidad Finis Terrae. Santiago, Chile.
[d]LARed Network. Santiago, Chile.
[e]Facultad de Ciencias de la Vida, Universidad Andres Bello. Santiago, Chile.
[f]Unidad Cuidados Intensivos Pediátricos, Clínica Alemana de Santiago. Santiago, Chile.
[g]Facultad de Medicina y Ciencia, Universidad San Sebastian. Concepcion, Chile.

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What do we know about the subject matter of this study?

Acute flaccid myelitis is an emerging neuromuscular disease affecting the spinal cord, mainly in children. It has been described since 2014 in North America.

What does this study contribute to what is already known?

We present 3 cases of acute flaccid myelitis secondary to Enterovirus, a severe disease not previously reported in our country, highlighting clinical keys to confirm the diagnosis.

Abstract

Acute flaccid myelitis (AFM) is a neuroinflammatory disease characterized by acute asymmetric weakness of the limbs associated with lesions of the gray matter of the spinal cord. It mainly affects children and has been increasingly identified since 2014. **Objective:** To describe a severe emerging neurological disease in Chile. **Clinical Case:** Three children (2 females), previously healthy were included. The age at the onset was between 4 and 6 years. All presented an acute febrile illness associated with upper respiratory symptoms, rapid onset of proximal asymmetric limb weakness, spinal fluid pleocytosis, and enterovirus isolated from nasopharyngeal swab; two patients developed tetraparesis. The MRI of the spinal cord showed T2 hyperintensity of the grey matter. The three patients were admitted to the Pediatric Intensive Care Unit (PICU), and two required mechanical ventilation. No significant improvements were observed after the use of immunomodulatory therapy and plasma exchange. At 12 months of follow-up, one case was quadriplegic and ventilator-dependent; the second died of ventricular arrhythmia in the PICU, and the third one is under rehabilitation with partial

Palabras clave:
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Correspondence:
Raúl Bustos B.
rbustos@sanatorioaleman.cl

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recovery. **Conclusions:** We report the first cases of this severe emerging neurological disease in our country. In a child with predominantly proximal and asymmetric acute limb paralysis, pediatricians must have a high index of suspicion for AFM. Since it can progress rapidly and lead to respiratory failure, suspected AFM should be considered a medical emergency.

Introduction

Acute flaccid myelitis (AFM) is a neuroinflammatory disease of the spinal cord mainly affecting children. It is characterized by the acute onset of flaccid paralysis of at least one limb, with asymmetric involvement of the proximal muscles in most cases. The US Center for Diseases Control and Prevention (CDC) started surveillance for this entity in August 2014, observing a peak of cases every two years, mainly between August and November, establishing a temporal relationship with enterovirus D68 (EV-D68) infections. To date, 679 cases have been confirmed[1,2]. AFM has also been described in case series in Europe, Japan, Argentina, and Australia[3-6].

The Council of State and Territorial Epidemiologists adopted a definition used by the CDC to classify patients as confirmed or probable cases of AFM, which was updated in June 2019[7]. Recently, the Acute Flaccid Myelitis Working Group has also proposed a confirmed case definition[8] (Tables 1a and 1b).

Clinical suspicion of AFM is critical for early treatment, given the risk of respiratory failure and complications resulting from dysautonomia. Unfortunately, there are no high-quality clinical trials for the treatment of AFM, however, several therapeutic strategies have been used in this disease without conclusive evidence of efficacy[9].

Our objective is to present three cases of AFM, an emerging severe pediatric neuromuscular disease in Chile.

Clinical Cases

Case 1

A previously healthy 4-year-old female preschooler, eutrophic and up-to-date immunizations, visited the emergency room due to decreased right arm movement, with a 3-day history of fever 39°C, cough, headache, and cervical pain. Physical examination revealed proximal right brachial palsy and mild dropped head syndrome, upper limbs hyporeflexia, absence of sensory involvement, and presence of meningism. Her vital signs and state of consciousness were normal, with no involvement of other systems.

She was admitted to the ICU due to suspected viral meningoencephalitis or stroke. All general laboratory tests were within normal range. The cerebrospinal fluid (CSF) showed pleocytosis (26 cells), 95% mononuclear cells. Empirical treatment with acyclovir and ceftriaxone was started and later discontinued since the multiple polymerase chain reaction (PCR) panel and CSF culture were negative. The respiratory viral panel by nasopharyngeal swab was positive for Enterovirus. Spine and brain MRI identified an increased signal in the T2 sequence of the gray matter of the spinal cord in the cervical region (C1 to C7), without cortical or central nuclei lesions (Figures 1a and 1b). The funduscopic examination was normal. She received methylprednisolone pulses (30 mg/kg) for five days, followed by oral prednisone. The patient did not present respiratory compromise during her hospital stay and did not require other therapies.

She was discharged six days later with a comprehensive outpatient rehabilitation program. After six months of follow-up, a slow recovery of the strength of the affected limb and cervical musculature was observed, achieving mobility of her affected limb in daily life activities.

Case 2

A 4-year-old male preschooler, previously healthy, and up-to-date immunizations, consulted due to right upper extremity paresis in November 2019. He presented with cough and coryza, headache, fever, and cervical pain five days before admission. Physical examination revealed proximal predominant right upper-limb weakness, hyporeflexia, meningism, and absence of sensory compromise. He was alert and oriented, and his vital signs were normal, with no other systems involved. He was admitted to the ICU due to suspected viral meningoencephalitis. CSF showed pleocytosis (70 cells), 55% mononuclear, and five erythrocytes. Empirical treatment with acyclovir was started, which was discontinued at 48h after a negative multiplex PCR panel and CSF culture. The respiratory viral panel by nasopharyngeal swab was positive for Enterovirus. MRI identified an increased signal in the T2 sequence of the gray matter of the lateral regions of the bulbomedullary junction, and the spinal cord in the C2 to C6 segments.

The patient developed flaccid tetraplegia and right upper limb paresis in less than 24 hours, requiring me-

Table 1a. Acute Flaccid Myelitis (AFM) 2020 Case Definition Council of State and Territorial Epidemiologists and adapted by the Centers for Disease Control and Prevention

Clinical Criteria
An illness with onset of acute flaccid weakness of one or more limbs
(Low muscle tone, limp, hanging loosely, not spastic or contracted) AND
Absence of a clear alternative diagnosis attributable to a nationally notifiable condition
Confirmatory laboratory/imaging evidence
MRI showing spinal cord lesion with predominant gray matter involvement† and spanning one or more vertebral segments. AND
Excluding persons with gray matter lesions in the spinal cord resulting from physician diagnosed malignancy, vascular disease, or anatomic abnormalities
†Terms in the spinal cord MRI report such as "affecting gray matter," "affecting the anterior horn or anterior horn cells," "affecting the central cord," "anterior myelitis," or "poliomyelitis" would all be consistent with this terminology.
Confirmed case
Clinically compatible case with confirmatory laboratory/imaging evidence, AND
Absence of a clear alternative diagnosis attributable to a nationally notifiable condition

Source: https://wwwn.cdc.gov/nndss/conditions/acute-flaccid-myelitis/case-definition/2020/

Table 1b. Diagnostic criteria for AFM according to Acute Flaccid Myelitis Working Group.

Clinical History
Acute onset of limb(s) weakness (period from onset to nadir: hours to 10 days).
Prodromal fever or illness.
Physical exam
Weakness involving one or more limbs, neck, face, or cranial nerves.
Decreased muscle tone in at least one weak limb.
Decreased or absent deep tendon reflexes in at least one weak limb.
MRI
Spinal cord lesion with predominant grey matter involvement, with or without nerve root enhancement
CSF
Pleocytosis (white cell count > 5 cel)

MR: magnetic resonance imaging, CSF: cerebrospinal fluid.

chanical ventilation (MV) due to respiratory failure. Video-EEG reported a slow baseline rhythm without epileptiform discharges. Aquaporin 4 and MOG antibodies in plasma were negative, and the funduscopic examination was normal.

He received intravenous immunoglobulin (IG) 2g/kg, followed by Methylprednisolone pulses (30 mg/kg) for five days, and then tapered off to oral prednisone according to protocol. Given the lack of improvement, plasma exchange (PLEX) was started, with seven sessions every other day. Since Neuromyelitis Optica

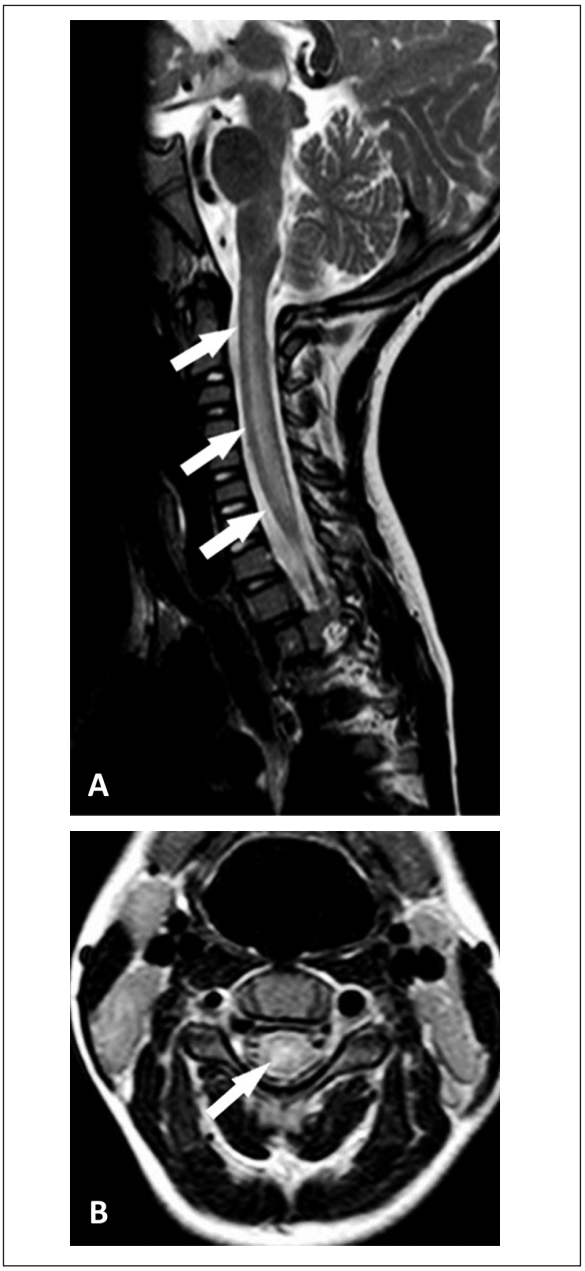

Figure 1. MRI findings in the acute phase of acute flaccid myelitis. **A**. Sagittal T2 at admission of case 1 with hyperintensity of the grey matter from C1 level to C7 (arrow) **B**. Axial T2 image showing hyperintensity of the grey matter.

refractory to standard treatment was considered the probable diagnosis, Rituximab was administered. Tracheostomy (TCT) and gastrostomy (GTT) were performed, considering long-term rehabilitation.

The patient remained conscious, obeying simple commands, and presenting asymmetric proximal tetraplegia. Motor impairment slowly and progressively improved over the following weeks, but severe cardiac dysautonomia was observed, especially arterial hypertension which appeared two weeks after the onset of neurological symptoms. Spinal cord MRI one month after admission reported almost complete regression of the lesions.

The patient presented ventricular fibrillation during a dysautonomia episode in the seventh week after admission. He did not respond to advanced resuscitation maneuvers and passed away with his parents' company.

Case 3

A previously healthy 3-year-old girl consulted the emergency department due to rhinorrhea, cough, and low-grade fever; after 24 hours since admission, she developed high fever of difficult management. On the second day of admission, she presented behavioral changes, irritability, and poor general condition. Photophobia, generalized muscle weakness, sialorrhea, and respiratory distress appeared on the fifth day.

On admission, she was alert and oriented with bilateral mydriasis, preserved pupillary light reflex, and generalized hypotonia with loss of trunk control. In addition, the patient presented polypnea, sialorrhea, dysphagia, Brudzinski's sign, upper limbs weakness, and hyporeflexia. Lower limb involvement was symmetrical.

She was diagnosed with asymmetric flaccid tetraplegia, therefore, she was admitted to the ICU for invasive MV. CSF showed 70 leukocytes with normal glucose and proteins. Aquaporin 4 antibody in plasma was negative. Viral and bacterial PCR in CSF were negative, but in nasopharyngeal swab was positive for Enterovirus. Electroencephalogram (EEG) and fundoscopic examination were normal. The spine MRI showed moderate enlargement of the spinal cord and increased enhancement of the intramedullary signal that extensively affected the gray matter. These alterations were mainly observed at the cervical level, extending between C2 and T8 with more intense areas in C2-C4 and T5-T8. After treatment with methylprednisolone 30mg/kg for five days, IG 2gr/kg, and four sessions of PLEX, she had no clinical improvement.

An MRI two weeks after admission showed longitudinally cervical-thoracic myelitis, with acute features plus polyradiculoneuropathy.

In addition, somatosensory evoked potentials and nerve conduction velocity performed two months after the beginning of symptoms showed motor compromise with denervation of the left upper limb. At that time, she had profound flaccid weakness in 4 limbs requiring GTT and TCT for permanent 24h a day chronic MV support.

She was discharged after four months with a home hospitalization program continuing with neurorehabilitation. She is currently eight years old, dependent on chronic MV support 24 hours a day, and bedridden with gross mobility of lower limbs, right-hand rotation, and left-hand paresis without cognitive compromise.

Table 2 summarizes the findings of the reported patients.

Discussion

To our knowledge, these are the first cases of AFM reported in Chile. They all meet the criteria established by the CDC and the Acute Flaccid Myelitis Working Group as confirmed cases of AFM[7,8].

It is important to highlight that all the children in our case report presented meningism, inflammatory CSF study, and asymmetric acute flaccid weakness with preserved state of consciousness. The age of presentation of AFM predominates in preschoolers and schoolchildren, and the key clinical characteristic was acute asymmetric weakness. The motor involvement is more pronounced in proximal areas and upper extremities ranging from single-limb paresis to tetraplegia.

Cranial nerve involvement may be present in up to 30% of cases, affecting the ocular, facial, and bulbar muscles[9]. Hypo/areflexia is frequent in the affected limbs, as well as the presence of a febrile respiratory prodrome and cervical or back pain before paralysis[10].

Some neurological diseases presenting with acute limb weakness and similar findings on MRI should be considered in the differential diagnosis, such as transverse myelitis, acute disseminated encephalomyelitis, and neuromyelitis optica. These diseases respond to immunotherapy, particularly corticosteroids or PLEX. In addition, spinal cord infarction can be suspected in patients with risk factors for stroke, trauma, and hyperacute presentation. Finally, Guillain Barre syndrome (GBS) has a particular clinical presentation of distal and ascending paralysis, sensory deficits, and CSF albumin/cytological dissociation without myelitis on spine MRI[11]. Table 3 summarizes the clinical and imaging features that could differentiate AFM from GBS and transverse myelitis.

Regarding complementary examinations, CSF analysis reveals moderate pleocytosis (up to 100 ele-

Table 2. Demographic, clinical, imaging characteristics and clinical course of the 3 cases presented

Demographic characteristics	1	2	3
Age	4y	4y 8mo	3y 7m
Sex	Female	Male	Female
Prodromal symptoms			
Days from onset of prodromal symptoms to weakness	3	5	5
Fever	Yes	Yes	Yes
Respiratory symptoms	No	No	Yes
Gastrointestinal symptoms	Yes	Yes	No
Neck pain	Yes	Yes	No
Enterovirus in nasopharingeal swab	Yes	Yes	Yes
Compromiso neurológico			
Limbs affected	Right upper limb	Four limbs	Four Limbs
Asymmetric limb weakness	Yes	Yes	Yes
Hyporeflexia/areflexia	Yes	Yes	Yes
Proximal dominance	Yes	Yes	Yes
Cranial nerve dysfunction	No	Bulbar weakness	No
Meningeal signs	Yes	Yes	Yes
Mechanical Ventilation requirement	No	Yes	Yes
Days from onset of weakness to hospitalization	1	1	1
CSF			
CSF pleocytosis (CSF WBCs/μL)	26	70	70
Identification of enteroviruses in CSF	No	No	No
MRI			
Localization of T2 spinal hyperintensity	C1-C7	C2-C6	C2-T8
Lession on brain MRI	No	No	No
Brainstem	No	Yes	No
Treatment administred			
Intravenous steroids	Yes	Yes	Yes
Intravenous immunoglobulin	No	Yes	Yes
Plasma exchange	No	Yes	Yes
Biological therapy	No	Rituximab	No
Response to treatment	None	None	None
Final diagnosis	Confirmed AFM	Confirmed AFM	Confirmed AFM
Prognosis of motor symptoms	Fair	Poor	Poor
Outcome	Alive	Death	Chronic MV

MV: Mechanical ventilation, CSF: cerebrospinal fluid, MRI: Magnetic resonance imaging, AFM: Acute Flaccid Myelitis.

ments), with lymphocyte predominance, and slightly increased or normal protein levels. As in our report, Enterovirus is identified in respiratory samples in most cases, followed by stool, and rarely in CSF[12]. Therefore, it is essential to emphasize the active search for Enterovirus since this finding may help for early diagnosis and treatment, avoiding unnecessary therapies such as PLEX.

MRI of the spinal cord is characterized by a hyperintense longitudinal lesion in the T2 sequence, affecting mainly the central gray matter, or more focally in the anterior grey column. The most common area affected is the cervical region, followed by the dorsal area and conus. Brain MRI may be normal but may also show T2 hyperintensities in the brainstem, including the dorsal pons, and occasional involvement of the dentate nucleus of the cerebellum[13].

The exact etiology of AFM is not yet entirely determined, but it is believed to be of viral origin since most confirmed cases are associated with an infectious prodrome (fever, upper respiratory, or gastrointestinal symptoms). Regarding the specific virus causing AFM, EV-D68 has been the main suspected agent, given its temporal and geographic association with outbreaks of

Table 3. Clinical, laboratory and imaging characteristics in acute flaccid myelitis, Guillain Barre syndrome and transverse myelitis

	Acute Flaccid Myelitis	Guillain Barre syndrome	Acute transverse myelitis
Prodrome			
Type	Febrile illness often with respiratory and/or gastrointestinal symptoms	Febrile illness often with gastrointestinal symptoms and or respiratory symptoms	Commonly a preceding febrile illness
Time until onset of weakness	Usually within 1 week	Several weeks	Days to weeks
Clinical details			
Neurologic deficits	Asymmetric flaccid weakness, with upper limbs often more affected, proximal > distal	Ascending weakness, lower limbs > upper limbs	Symmetric weakness, may be asymmetric initially
Reflexes	Typically low or absent	Low or absent	Usually high, can be low initially
Sensory symptoms	Typically no sensory deficits	Paresthesia and slight distal sensory symptoms (except in AMAN)	Common, often with a sensory level
Cranial nerve deficits	Bulbar weakness and asymmetric facial palsy common; sometimes oculomotor deficits	Symmetric facial weakness; oculomotor deficits in MFS	None
Other symptoms	Pain, autonomic dysfunction	Pain, autonomic dysfunction	Bowel and bladder dysfunction
Time course	Progressive over hours to days	Progressive symptoms over several days	Progressive over 4 h to 21 days
Findings			
CSF	Slight pleocytosis, raised protein. May be completely normal	Raised protein after several days, without pleocytosis	Slight pleocytosis, raised protein. May be completely normal
Microbiology	EV-D68 in respiratory specimen	*Campylobacter jejuni* in feces	Usually none
MRI brain	Typical T2-hyperintense region in the dorsal pons, sometimes also in caudate nuclei. Cranial nerve enhancement possible	Normal	Normal
MRI spine	Longitudinally extensive diffuse slightly hyperintense central cord lesion, usually in the cervical region. Sometimes cauda equina root enhancement	Cauda equina root enhancement may be found	Central cord focal hyperintense lesion over multiple levels affecting white and gray matter
EMG	Findings of motor axonopathy with low CMAPs, normal NCV. Normal sensory findings	Decreased NCV with blocks are typical. Normal sensory findings in AMAN	Normal
Serum MOG, aquaporin-4 antibody	Negative	Negative	Could be positive
Treatment/prognosis			
Treatment	No effective treatment, potential positive effect of IVIG	IVIG and/or plasmapheresis effective	High-dose steroids, sometimes IVIG and/or plasmapheresis
Prognosis	Improvement over several months, significant residual weakness and muscle atrophy	Often complete recovery over the course of weeks until months	Partial recovery over the course of months until years

IVIG: intravenous immunoglobulin, NCV: nerve conduction velocity, EMG: electromyography, CSF: cerebrospinal fluid, EV-D68: enterovirus D68, MRI: magnetic resonance imaging, MF: Miller Fisher syndrome. CMAP: compound muscle action potential, AMAN: acute motor axonal neuropathy, MOG: myelin-associated oligodendrocyte glycoprotein.

AFM cases in the USA. Furthermore, two recent studies using the Bradford Hill criteria (strength of association, consistency, temporality, biological plausibility, coherence criteria, experimental evidence, and analogy) have established a causal relationship between EV-D68 and AFM[14,15].

Some potentially pathogenic mechanisms of this condition have been postulated, including direct viral damage, spinal cord damage secondary to the antiviral immune response, and host genetic factors. However, experimental models support the first hypothesis since neurotropism of EV-D68 by motor neurons of the spinal cord has been observed, causing paralysis. EV-D68 strains from the 2014 outbreak caused paralysis in an animal model, while EV-D68 isolated from the spinal cord of already paralyzed animals managed to transmit flaccid weakness to animals not previously exposed to the virus[16].

Currently, there is no known effective therapy for this disease, so most affected patients have partial motor recovery or permanent disability, despite intensive rehabilitation programs. The CDC clinical guidelines for the treatment of AFM conclude that there is not enough evidence to recommend or rule out a specific treatment[17]. Patients with AFM have been treated with a combination of IG, high-dose steroids, and/or PLEX, with no correlation between these treatments and improved outcomes[18].

In the cases presented, the use of high-dose steroids was motivated by spinal edema on MRI and the uncertainty of the initial diagnosis. In an experimental model of EV-D68 myelitis, the administration of IG on day one post-infection protected against paralysis, however, the effect was attenuated if administered between days 3 and 6 post-infection, suggesting that its efficacy could be time-dependent. In this same model, there was lower mortality and viral load in the spinal cord in subjects treated with IG[18]. Although the presence of neutralizing antibodies against EV-D68 has been confirmed in commercially available IG, clinical experience has not shown clear evidence of better outcomes[19]. PLEX has been used in refractory cases of AFM without evidence of clinical benefit. On the contrary, PLEX could be deleterious because of the possibility of "sweeping" possible antibodies against Enterovirus[20].

The lack of response observed with immunotherapy in the acute treatment of AFM would support the theory that AFM may be related to a direct viral infection rather than an autoimmune phenomenon. However, given the lack of clarity in the pathophysiology of this disease, immunomodulatory treatment continues to be used empirically. In addition, the experimental use of fluoxetine, which has anti-enteroviral properties in vitro, has also been reported, however, a retrospective study in 56 patients in 12 USA centers showed no improvement in neurological outcomes after initiating treatment five days after symptom onset[21].

Chronic treatment of AFM is multidisciplinary, and physical and occupational therapy are essential to recovering functionality and muscle strength and reducing pain and deformity of the affected limbs. Recent data suggest that patients with AFM show functional improvement with continued rehabilitation therapy[22].

A surgical approach to the treatment of AFM sequelae has been proposed, consisting of nerve transfer. In 16 children with AFM who did not recover upper extremity mobility after six months, this surgery allowed recovery of elbow mobility in 87% of cases[23].

Regarding outcomes, most patients present persistent motor deficit, with isolated cases of immediate recovery. Proximal muscle strength seems to be the slowest to recover. Recovery time is variable, with some patients demonstrating continued improvement after 12 months from the onset of symptoms[24,25].

Conclusion

Pediatricians should have a high suspicion index for AFM in a child with acute proximal predominantly asymmetric flaccid weakness with meningism and inflammatory CSF. Since AFM can progress rapidly and lead to respiratory failure, suspected AFM should be considered a medical emergency, and the patient should be hospitalized in the ICU. In addition, multicenter studies are required to further investigate the pathophysiological mechanisms and risk factors that predispose some children to present acute flaccid weakness after viral infection and to evaluate the efficacy of different treatments and rehabilitation modalities for this type of myelitis.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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