Exploring the Phenotypic Profile of Acute Flaccid Paralysis: Insights from a Third-Level Pediatric Emergency Room

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ABSTRACT

Objectives

Acute Flaccid Paralysis (AFP) in children can stem from a diverse array of potential diagnoses.

Materials & Methods

This retrospective study sought to diagnose children referred to a referral pediatric emergency unit with AFP between 2011 and 2016. The study gathered clinical observations, conducted stool and cerebrospinal fluid analyses, and assessed electrophysiological and imaging data.

Results

The present study enrolled 118 fully immunized children with a mean age of 6.09 ± 3.60

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years. The most prevalent diagnoses included Guillain-Barré Syndrome (GBS-80 cases), acute viral myositis (20 cases), Transverse Myelitis Syndrome (TMS) (TMS-6 cases), and Vaccine-Associated Paralytic Poliomyelitis (VAPP) (VAPP-6 cases). All these six patients had primary immunodeficiency. Notably, all patients tested negative for poliovirus in stool analyses. This study encountered a unique case of a 2.5-month-old male patient who presented with acute limb motor weakness, along with fever, irritability, new-onset hypotonia, and generalized decreased deep tendon reflexes. Notably, no signs of upper motor neuron involvement were found. The Cerebrospinal Fluid (CSF) analysis was compatible with the diagnosis of viral meningitis. Moreover, among the 60 brain and spinal imaging series performed, five were indicative of GBS, six cases showed evidence of TMS, and one revealed a spinal mass. Besides, clinical investigations pointed toward acute viral myositis as a secondary etiology of AFP in 20 patients in this study.

Conclusion

In this hospital-based study, the most frequent diagnoses for children arriving at a third-level pediatric Emergency Room (ER) with acute flaccid paralysis AFP were GBS, acute viral myositis, TMS, and VAPP). These findings suggest a distinct pattern of AFP causes compared to those found in community-based epidemiological studies. Additionally, notably, unusual conditions, such as viral meningitis, can rarely present with AFP-like symptoms. Assessment for primary immune deficiency should be considered in cases of VAPP. Lastly, this research has implemented a pediatric AFP Management Protocol: A Local Practical Approach.

Introduction

The World Health Organization (WHO) defines Acute Flaccid Paralysis (AFP) as a complex clinical condition characterized by the sudden onset of weakness in one or more limbs, which may progress to affect respiratory and swallowing muscles, reaching maximum severity within days to weeks (1, 2). The estimated annual incidence of AFP in children under 15 is one in 100,000 (2). The term “flaccid” indicates the absence of upper motor neuron signs, predominantly affecting the motor portion of the spinal cord, excluding traumatic causes (3). AFP may also have coordination and gait problems (2, 4).

AFP can stem from a variety of underlying conditions. These include:

- **Acute poliomyelitis**: caused by poliovirus or other neurotropic viruses and can also result from Vaccine-Associated Paralytic Poliomyelitis (VAPP).
- **Acute myelopathy**: this can be due to conditions like space-occupying lesions, spinal shock, or Transverse Myelitis Syndrome (TMS).
- **Peripheral neuropathy**: such as Guillain-Barre Syndrome (GBS).
- **Systemic diseases**: include acute intermittent porphyria and critical illness myopathy.
- **Neuromuscular junction disorders**: like myasthenia gravis and botulism.

Muscle disorders: include inflammatory myopathy (polymyositis), acute viral myositis, and periodic paralysis.

Understanding the diverse causes of AFP is essential for accurate diagnosis and treatment (1, 4, 5). Timely and accurate diagnosis and treatment of the underlying condition are crucial because untreated AFP can lead to severe adverse outcomes, including prolonged neurological complications, motor impairment, or even death due to respiratory muscle failure (6, 7).

According to reports from the Global Polio Eradication Initiative (GPEI), there has been a remarkable decline in polio incidence worldwide over the last two decades, largely thanks to routine poliovirus vaccination. Consequently, GBS has replaced poliomyelitis as the most common cause of AFP (1, 8). Additionally, a subtype known as Acute Flaccid Myelitis (AFM) has emerged in recent spikes of AFP cases in the US. AFM patients displayed abnormal signals in the gray matter of spinal imaging, along with evidence of non-polio enterovirus EV-D68 infection in respiratory secretions (9). Numerous studies conducted in various provinces of Iran in the past 25 years have consistently identified GBS as the primary cause of AFP, aligning with global trends (10-12). Notably, since a single case of polio in 1997, no further cases have been reported in Iran (13).

The current study aimed to identify primary diagnoses in children presenting with acute motor limb weakness or AFP at the main referral pediatric Emergency Room (ER) at Children's Medical Center (CMC-ER) in Iran between 2011 and 2016. The main objective was to comprehensively describe clinical, imaging, and laboratory findings among these patients and to propose a local AFP Management Protocol in the pediatric ER.

Material & Methods

Study design

This retrospective cross-sectional study utilized data from the CMC-ER registry system, the primary referral children's hospital in Iran, covering the period from 2011 to 2016. Diagnoses in the registry were categorized using the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM). This study included all patients under 15 who presented to the CMC-ER with clinical symptoms of AFP, acute motor limb weakness, coordination difficulties, or gait problems. The study protocol received approval from the Ethical Committee of Tehran University of Medical Sciences (approval code: IR.TUMS.MEDICINE.REC.1396.3122), and written informed consent was obtained from parents or legal guardians for their children's participation in the study.

Participants and data collection

The present study included children and adolescents who met the WHO criteria for AFP or exhibited symptoms of acute motor limb weakness, coordination difficulties, gait problems, or a combination. Children whose parents were unwilling to provide documentation or had incomplete medical records were excluded from the study.

This study conducted a retrospective assessment of the phenotypic characteristics of the enrolled patients, encompassing their demographic information, immunization status, initial clinical symptoms, laboratory findings, and neuroimaging results. Clinical symptoms were categorized into two groups: constitutional symptoms, including fever, coryza, diarrhea, nausea, vomiting, and

myalgia; and neurological symptoms, comprising motor and sensory impairment, autonomic dysfunction (particularly bowel and bladder dysfunction), meningeal irritation symptoms, and signs of anterior horn cell damage, such as fasciculation. The neurological examination data were evaluated, focusing on distinguishing between focal and generalized motor weakness or flaccidity and assessing deep tendon reflexes (DTRs).

In compliance with WHO guidelines, the researchers collected data related to stool sample analysis from all AFP patients. This involved the collection of two stool samples, taken 24-48 hours apart within 14 days of the onset of paralysis, to assess for the presence of poliovirus. Additionally, this study meticulously considered potential AFP mimics, including drug intoxication, Acute Cerebellar Ataxia (ACA), orthopedic conditions, and chronic systemic diseases. In such cases, the researchers gathered necessary laboratory test results, including urine toxicology. Patients diagnosed with an AFP mimic were subsequently excluded from the study.

For cases of acute viral myositis, this study collected data on serum Creatine Phosphokinase (CPK) and aldolase levels when available. In instances of GBS or when Central Nervous System (CNS) infection was considered an AFP mimic, this research scrutinized Cerebrospinal Fluid (CSF) analyses. Furthermore, this study included data on electrophysiological findings, encompassing Electromyography (EMG) and Nerve Conduction Velocity (NCV) results, conducted in patients exhibiting lower motor neuron signs. These tests aided in distinguishing between various neuromuscular disorders, such as demyelinating neuropathy, axonal neuropathy, neuromuscular junction disorders, preganglionic lesions, myopathies, and anterior horn cell disorders (Supplementary Method 1). The diagnosis of GBS was established based on clinical findings corroborated by CSF albumin-cytologic dissociation and/or evidence of demyelination or axonal damage as observed in EMG-NCV studies. Finally, this research also considered all neuroimaging data, including brain and spinal Magnetic Resonance Imaging (MRI) and/or Computed Tomography (CT) scans.

Statistical analysis

The data were analyzed using SPSS Version 25 software. The mean ± SD was used to describe quantitative variables such as the age of patients, and the like, while the number and percent were used to describe qualitative variables.

Results

Demographic data and the spectrum of etiologies

During this five-year study, the researchers identified 118 patients who met the inclusion criteria. Among them, 77 (65.3%) were males, and 41 (34.7%) were females. The mean age of the enrolled patients was 6.09 ± 3.60 years. The most common underlying etiologies were GBS and acute viral myositis, accounting for 80 cases (67.8%) and 20 cases (16.9%). Notably, this study detects no confirmed cases of wild-type poliomyelitis. However, six cases (5.1%) were found to be diagnosed with VAPP. Further investigations into these six patients revealed primary immunodeficiency, with diagnoses including X-Linked agammaglobulinemia (XLA) in three cases, Severe Combined Immune Deficiency (SCID) in two cases, and Common Variable Immunodeficiency (CVID) in one case. The prevalence of various etiologies of AFP in

these patients is detailed in Table 1.

Clinical manifestations

In terms of constitutional symptoms, 66 patients (55.9%) reported coryza, 46 patients (39%) had a fever, and 18 patients (15.3%) experienced gastrointestinal symptoms such as diarrhea, nausea, and vomiting. Among the neurological symptoms, 112 cases (94.9%) presented with acute motor deficits, encompassing acute motor weakness, flaccid limb weakness, difficulty in coordination, and gait disturbance. Autonomic dysfunction-related symptoms were reported in 43 patients (37.3%), including pain in 36 out of 43 cases (84%), sphincter dysfunction in 6 out of 43 cases (14%), and palpitations in 1 out of 43 cases (2.3%). Sensory symptoms were observed in 11 patients (9.3%). Among patients diagnosed with GBS, autonomic symptoms were the most frequently reported.

Among patients with acute motor deficits, generalized motor weakness or flaccidity was identified in 47.5% of cases, while pure lower limb involvement was observed in 40.7%, and pure upper limb involvement occurred in 0.8% of cases. Decreased deep tendon reflexes (+1/4) were reported in 84.7% of patients. The average duration between the onset of motor deficit and hospitalization was four days. Acute flaccid limb weakness, or AFP, was more commonly observed in winter and spring.

Laboratory and imaging findings

Two stool samples were sent to the reference laboratory to detect the poliovirus in 80% of cases, but all results returned negative. In 97.5% of stool samples, the results were either normal or nonspecific. However, in 2.5% of cases, botulinum toxin was detected.

CSF analysis was conducted in 70 out of 80 patients clinically diagnosed with GBS. The CSF results supported GBS in 58 patients, with a mean CSF protein level of 78 mg/dl (normal <45 mg/dl), a mean White Cell Count (WBC) of 4 (normal: <5/mm3), and a glucose level of 61 mg/dl (normal: >50 mg/dl). In the remaining cases without CSF analysis or with negative results, the diagnosis of GBS was based on a combination of clinical

Table 1. Etiologies of AFP in patients

Diagnosis	Frequency (percentage)
Guillain-Barre syndrome (GBS)	80 (67.8%)
Acute viral myositis	20 (16.9%)
Transverse myelitis syndrome (TMS)	6 (5.1%)
Vaccine-associated paralytic poliomyelitis (VAAP)	6 (5.1%)
Botulism	3 (2.5%)
Periodic Paralysis	2 (1.7%)
Spinal mass lesion	1 (0.8%)
Total	118 (100%)

symptoms and EMG-NCV findings. Remarkably, a 2.5-month-old male patient presented with acute limb motor weakness, fever, irritability, and decreased DTRs, but his CSF results indicated viral meningitis (positive adenovirus polymerase chain reaction (PCR) in CSF; glucose level of 35/mm3, protein level of 88 mg/dl, and WBC count of 21/mm3 with 85% lymphocytes; negative bacterial smear and culture).

In total, 79 patients underwent EMG and NCV studies, with results favoring GBS in 61 cases, mostly showing demyelinating neuropathy. The mean NCV level was 38 m/s (36.4-39.6 m/s), which fell below the normal limit (Table 2). EMG-NCV was performed in four out of 20 patients with a final diagnosis of acute viral myositis, with findings compatible with myopathic changes in one patient and expected results in three patients. Notably, serum CPK levels were assessed before electrophysiological studies. In only one out of three cases of botulism, EMG-NCV was conducted, revealing findings consistent with a neuromuscular junction disorder. In all three patients with botulism, stool examinations were positive for botulinum toxin.

Brain CT scans and spinal MRIs were conducted

Table 2. Electromyography and Nerve Conduction Velocity (EMG-NCV) findings in patients

Clinical diagnosis (n=79)	EMG-NCV Pattern Frequency (Percentage)					
	Normal	Demyelination neuropathy	Axonal neuropathy	NMJ dysfunction	Anterior horn cell disorder	Myopathic process
Guillain-Barre Syndrome (65/79, 82.3%)	4/65 (6.16%)	40/65 (61.54%)	21/65 (32.3%)	-	-	-
VAPP (4/79, 5.07%)	-	1/4 (25%)	-	-	3/4 (75%)	-
Acute viral myositis (4/79, 3.8%)	3/4 (75%)	-	-	-	-	1/4 (25%)
Transverse myelitis (2/79, 2.53%)	-	-	-	-	2/2 (100%)	-
Botulism (1/79, 1.26%)	-	-	-	1/1 (100%)	-	-
Periodic paralysis (1/79, 1.26%)	1/1 (100%)	-	-	-	-	-
Spinal mass lesion (1/79, 1.26%)	-	-	-	-	1/1 (100%)	-
Viral meningitis (1/79, 1.26%)	-	-	-	-	1/1 (100%)	-
Total (N= 79, 100%)	8/79 (10.12%)	41/79 (51.9%)	21/79 (26.6%)	1/79 (1.26%)	7/79 (8.86%)	1/79 (1.26%)

Abbreviations: EMG-NCV; Electromyography and Nerve Conduction Velocity, NMJ dysfunction; Neuromuscular junction dysfunction, VAPP; Vaccine-associated paralytic poliomyelitis

in 14 and 46 patients, respectively, based on presenting symptoms and neurological exams to rule out potential CNS pathologies. All brain CT scans returned normal results. Among the 46 patients who underwent spinal MRI, five exhibited surface thickening and marked enhancement in the anterior spinal cord nerve roots, particularly in the conus medullaris and cauda equina, indicative of GBS. In six patients, T2-weighted signal changes of varying size and extent were also detected, favoring TMS. In one patient, a spinal mass in the lumbosacral region was discovered and confirmed as a spinal astrocytoma following pathology investigations.

Additionally, an elevated serum CPK level, reaching up to 2700 IU/L, was observed in 20 patients with acute lower limb motor weakness and muscle pain following a febrile viral infection, suggesting acute viral myositis (normal: <195 IU/L). Importantly, a follow-up visit four weeks after disease onset revealed significant improvement in motor weakness and muscle pain in all 20 patients, reducing the likelihood of other inflammatory myopathy caused by a chronic clinical course, such as polymyositis or hereditary myopathy.

Discussion

This cross-sectional retrospective study evaluated 118 patients with clinical symptoms, including AFP, acute motor limb weakness, gait disturbance, or a combination of these. The present assessment encompassed demographic, clinical, and paraclinical findings, as well as the final diagnosis.

The average age of the patients was 6.09 ± 3.60 years old, with 44.9% falling within the 5-10-year age group and 37.3% under the age of 5. Notably, the most common age range for children with AFP has been reported as under five years old in previous studies (4, 7-10, 14). Gender differences, as well as the distinction between systemic and neurological manifestations and physical examination findings, were consistent with previous research (1, 7, 8, 10, 14). In the current study, the four most common diagnoses were GBS, acute viral myositis, TMS, and VAPP. GBS was the most prevalent etiology, aligning with prior reports (1, 2, 7, 9, 14). Given GBS's treatable nature, a favorable prognosis can be expected for most cases of AFP in children. Moreover, the higher prevalence of AFP during the winter and spring seasons may be attributed to the increased incidence of respiratory infections, potentially contributing to the onset of GBS. Regarding other causes of AFP, acute viral myositis emerged as the second most common etiology in our study, in line with findings from Momen et al. and Zeeiouh et al. (14, 15). Notably, the WHO and most community-based childhood studies consider acute viral myositis as a cause of AFP (1, 4, 10-12, 14-17). However, in a few studies where acute viral myositis was not considered, TMS was reported as the second most common cause of AFP (18, 19). Given the significant prevalence of acute viral myositis in our study, there appears to be a strong case for including this entity in the clinical approach to AFP or acute motor limb weakness in pediatric ERs.

While muscle pain, tenderness, and difficulty walking following an acute febrile viral infection commonly present in acute viral myositis, our patients who received this diagnosis often had lower limb motor weakness as a predominant symptom. Therefore, it may be prudent to consider assessing acute viral myositis using biomarkers such as serum CPK and aldolase in the diagnostic

approach to AFP or acute motor limb weakness, especially in highly suspicious cases (8, 10, 12, 16, 17). Remarkably, all 20 patients diagnosed with acute viral myositis showed complete recovery with no residual neurological deficits at the 4-week follow-up visit, supporting this diagnosis over chronic inflammatory muscular disorders like polymyositis or hereditary myopathies. While a combination of clinical and paraclinical findings has been suggested for diagnosing acute viral myositis, the absence of diagnostic criteria with reasonable sensitivity and specificity presents a significant challenge (16, 20, 21) (18). This study did not repeat the EMG-NCV study or serum CPK levels in patients with this diagnosis, as their conditions improved significantly during the follow-up visit. Furthermore, this study did not perform viral serology or PCR on nasal or throat secretions to identify the specific viral etiology associated with their clinical diagnosis. Documentedly, various viruses can lead to acute viral myositis by affecting the anterior horn cells (22). Poliomyelitis, caused by the poliovirus, was the most prevalent cause before implementing effective vaccination strategies (23). However, since 2014, cases have often been linked to non-polio enteroviruses (24-26), as well as other types of viruses (27-29).

To the best of our knowledge, no cases of VAPP have been reported in previous studies from Iran. The present study, conducted in a large referral pediatric hospital with access to advanced diagnostic facilities, such as the Immune Deficiency Research Center, enabled us to make these diagnoses (12, 30, 31). In a recent surveillance of AFP in Italy, VAPP was identified as a potential cause in two cases (32).

The current research study did not identify any cases of poliomyelitis, which is consistent with the results of national studies on AFP in Iran since 1997, marking the last reported case of poliomyelitis in the country (13). However, several Middle Eastern countries still pose a high risk for poliomyelitis due to limited vaccination coverage and migration trends within these regions (13, 33). In contrast, other countries like Iran, Belarus, Italy, and Japan have not reported any cases of poliomyelitis (4, 31, 32, 34, 35). Importantly, stool sample analysis for detecting poliovirus was conducted following WHO guidelines. However, the limited availability of stool sample results for poliovirus in 80% of patients posed a limitation in our study, primarily due to factors such as early patient discharge or the inability to collect stool samples, often related to constipation.

Conversely, this study did not report any cases of traumatic neuritis following injection, even though some studies have mentioned it as a potential common cause of AFP (1, 12, 35). Various population-based studies have reported a diverse spectrum of causes for AFP. Interestingly, CNS infection has not been commonly identified as a direct cause of AFP, although it can exhibit AFP-like symptoms, as noted in some epidemiological studies (11, 12, 35). This study encountered a unique case of a 2.5-month-old male patient who presented with acute limb motor weakness, along with fever, irritability, new-onset hypotonia, and generalized decreased DTRs. Notably, no signs of upper motor neuron involvement were observed. The CSFs analysis was consistent with the diagnosis of viral meningitis. EMG-NCV findings indicated anterior horn cell disease. However, brain CT scans and other laboratory investigations yielded the expected results. This case underscores the fact that CNS infections can indeed mimic AFP. However, a precise evaluation of the patient and consideration of an LP can lead to the correct

diagnosis. Various conditions, including acute cerebellar ataxia (ACA), orthopedic issues, drug intoxication, and chronic systemic diseases, have the potential to mimic AFP. A thorough history and examination are valuable tools for ruling out these AFP imitators. Excluding AFP imitators based on history and examination findings is a reasonable approach. However, remarkably, this study did not delve into a detailed examination of AFP imitators.

Considering the normal results of neuroimaging in the majority of our patients (48 out of 60, 80%), including brain CT-Scans and spinal MRIs, it can be inferred that neuroimaging may offer valuable insights primarily in highly selective cases where patients present with alarming neurological examination findings. These concerning signs may include upper motor neuron signs, focal neurological deficits, sphincter dysfunction, spinal tenderness, sensory disturbances, or the presence of a sensory level. Neuroimaging serves a crucial role in ruling out conditions such as spinal cord compression, TMS, myelopathy, neoplasms, or traumatic neuritis (1, 12). Finally, the current study has introduced a pediatric AFP Management Protocol: A Local Practical Approach. This algorithm considers this study's findings and the most significant etiologies of AFP, aiming to assist healthcare providers in pediatric ERs in adopting a more precise assessment strategy for each patient (Fig. 1).

The present study has several limitations to consider. First, the data were collected from a single tertiary care hospital, which may limit the findings' generalizability to population-based studies. Second, this study primarily focused on diagnosis rather than long-term patient follow-up. Additionally, the absence of paraclinical data, such as stool and CSF analysis and spinal MRI results in some patients, could introduce bias in interpreting the results.

In Conclusion

In summary, the most common diagnoses among children presenting to a third-level pediatric ER with AFP were GBS, acute viral myositis, TMS, and VAPP. The hospital setting may reveal a distinct pattern of AFP etiologies, including recognizing acute viral myositis as a noteworthy cause. Additionally, notably, unusual conditions, such as viral meningitis, can rarely present with AFP-like symptoms.

Acknowledgments

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Authors' Contributions

All authors contributed to the study conception and design and drafted the work. Material preparation, data collection, and analysis were performed by Mahmoud Reza Ashrafi, Maryam Bemanalizadeh, Masood Ghahvechi Akbari, Sanaz Rezaei, Nima Parvaneh, Morteza Heidari, Mohammad Vafaee-Shahi, Firouzeh Hosseini, Sayna Bagheri. Sareh Hosseinpour and Roxana Pazouki contributed to the critically revised manuscript. All authors commented on previous versions of the manuscript. Ali Reza Tavasoli contributed to the interpretation and acquisition of the data and participated in the critical review of the final manuscript. All authors read and approved the final manuscript and agree

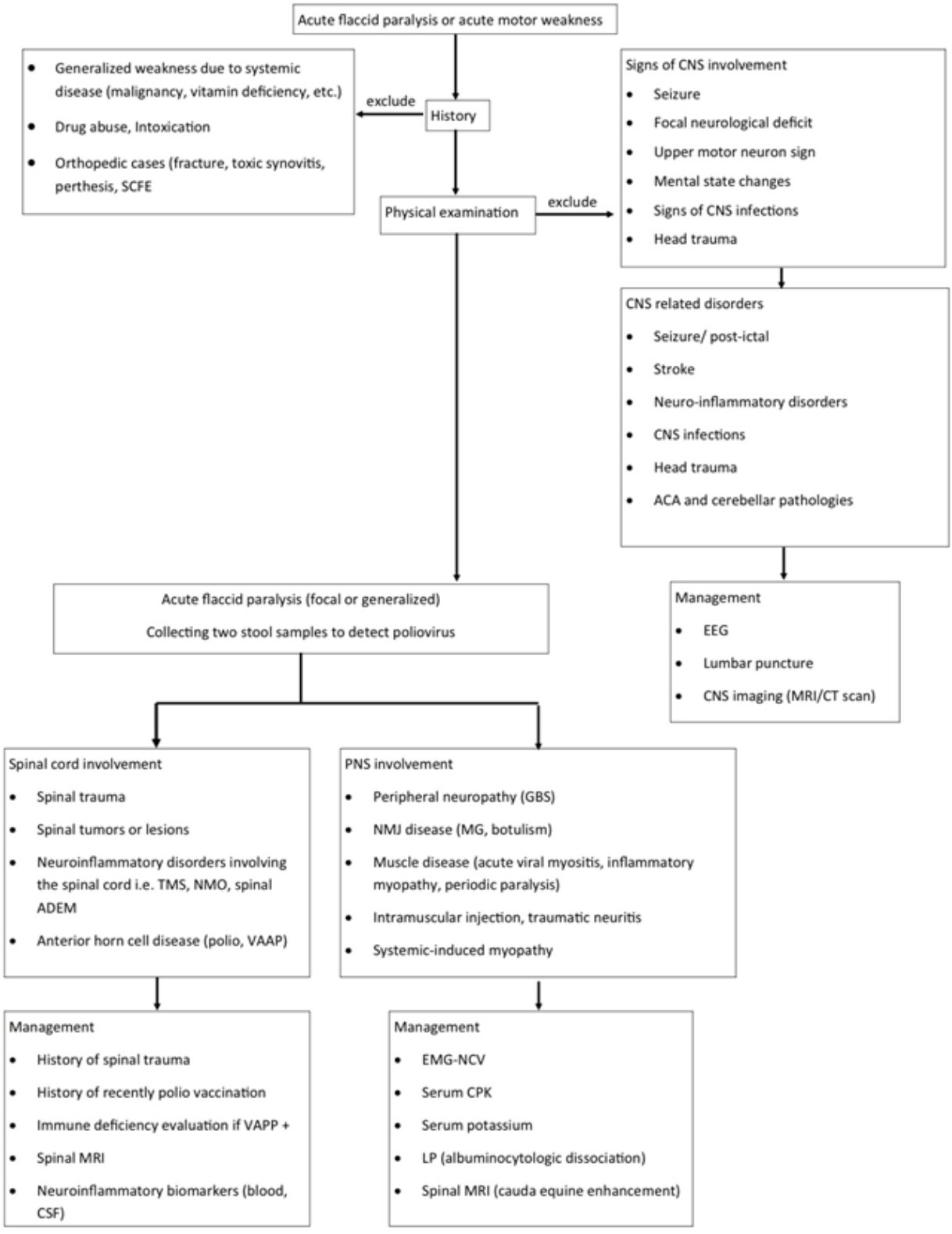

Figure 1. Pediatric AFP Management Protocol: A Local Practical Approach

AFP: Acute flaccid paralysis, SCFE: Slipped capital femoral epiphysis, ACA: Acute Cerebellar Ataxia, CNS: Central nervous system, TMS: Transverse Myelitis Syndrome, NMO: Neuromyelitis Optica, ADEM: Acute Disseminated Encephalomyelitis, PNS: Peripheral Nervous System, GBS: Guillain-Barre Syndrome, NMJ disease: Neuromuscular junction disease, MG: Myasthenia Gravis, VAPP: Vaccine-Associated Paralytic Poliomyelitis, EMG-NCV: Electromyography and Nerve Conduction Velocity, EEG: Electroencephalogram, CPK: Creatine Phosphokinase, LP: Lumbar puncture, MRI: Magnetic Resonance Imaging

to be accountable for all aspects of the work to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of Interest

The authors have no relevant financial or non-financial interests to disclose.

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