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Causes and outcomes of hypotonia: a cross-sectional study of children admitted to a pediatric intensive care unit

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Abstract: **Objective:** Hypotonia in children is an important and common clinical symptom that can manifest in various neurological disorders. It often poses a serious diagnostic challenge for physicians, frequently leading to inaccurate evaluations and unnecessary investigations. The purpose of this study was to investigate the causes of hypotonia, various diagnostic methods, and the final outcomes of these patients.

Methods: Children with hypotonia who were hospitalized in the pediatric intensive care unit (PICU) of Bahrami Children's Hospital and Children's Medical Center during a two-year period (2017-2018) were enrolled. All relevant information, including key points from their medical history, clinical examinations, and paraclinical data that could lead to diagnosis, were recorded. The patients was followed up for two years after hospitalization through phone calls or visits to the neurology clinic.

Results: Out of 65 children examined, 28 patients (43.07%) had peripheral nervous system involvement, 20 (30.76%) had central nervous system involvement, and 4 (6.17%) had both central and peripheral nervous system involvement. The most common causes for peripheral and central involvement were spinal muscular atrophy (SMA) and syndromic causes, respectively. In 20% of cases however an, specific underlying cause was found. The most common diagnoses were SMA (16.9%) and Guillain-Barre syndrome (13.8%). Finally, 15 children (23.1%) recovered, 31 (47.7%) had neurological sequelae, and 19 (29.2%) died.

Conclusion: Understanding the underlying causes and outcomes of patients hospitalized with hypotonia in the PICU enhances physicians' diagnostic skills. It is also useful for selecting effective treatment strategies and avoiding the complications associated with delayed diagnosis.

Keywords: Children; Etiology; Hypotonia; Intensive Care Unit; Outcome

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1. Introduction

The list of disorders that can lead to hypotonia during infancy and childhood is extensive, and the diagnostic process is often complex.

Understanding the relative prevalence of these disorders will help in selecting appropriate diagnostic methods (1). Hypotonia is a symptom found in a wide range of diseases that may affect any level of the nervous system. These disorders can be classified into two major groups: central hypotonia, which involves the upper motor neuron (brain, brainstem, and cervical spinal cord junction), and peripheral hypotonia, which involves the lower motor neuron (anterior horn cells of the spinal cord, peripheral nerve, nerve-muscle junction, and muscle) (1-3). The primary role of the neurologist at the patient's bedside is to differentiate between central and peripheral nervous system involvement, enabling the selection of appropriate diagnostic methods (2). Numerous genetic and neurological diseases contribute to infantile hypotonia (2). While previous studies have evaluated the causes of hypotonia in outpatient children (1-3), there is limited research specifically focused on hypotonia in children hospitalized in the pediatric intensive care unit (PICU). Given the seriousness and diverse etiology of these disorders, we aimed to identify the most common causes and outcomes of severe

hypotonia in children leading to hospitalization in the PICU. This approach will contribute to reducing misdiagnosis by facilitating physicians to select the most appropriate and accurate diagnostic method.

2. Methods

2.1. Study design

This is a cross-sectional study.

2.2. Study population

Children aged one month to 18 years with generalized hypotonia, admitted to the PICU of Bahrami Children's Hospital and Children's Medical Center at the time period of two years (2017-2018). The diagnosis of hypotonia in these patients was confirmed by a pediatric neurologist.

2.3. Inclusion criteria

Patients aged one month to 18 years admitted to the PICU with complaints of generalized hypotonia or hypotonia as one of the primary manifestations of their disease were included. Hypotonia was defined as the absence of resistance to passive movements and its diagnosis was confirmed by a pediatric neurologist.

2.4. Exclusion criteria

Exclusion criteria included parents' lack of consent to participate in the study, uncertainty regarding the diagnosis of hypotonia, and hypotonia secondary to drug use.

2.5. Sample size

The study determined the sample size using a census method and based it on the cross-sectional retrospective nature of the study. All eligible patients were included in the study over a 2-year period. The sample size of 65 cases was similar to that of previous articles (3-7).

The study began with obtaining informed consent from the parents of eligible children for their participation. A checklist was then prepared to record all demographic information (such as age, gender, parent's consanguinity, history of other child's death, family history of illness, history of drug use, and history of head trauma) as well as important data from their medical history and clinical examination. The decision to perform paraclinical methods was based on the clinical judgment of the physician. Patients with evidence of central nervous system involvement underwent magnetic resonance imaging (MRI), while those with peripheral nervous system involvement underwent electromyography and nerve conduction velocity (EMG-NCV) testing. In cases where the past medical history, family history, or history of death in a sibling suggested the presence of a congenital metabolic disease, relevant tests were requested. The results of paraclinical methods, including laboratory studies, neuroimaging (such as MRI), EMG-NCV, genetic studies, and muscle biopsy were recorded for each patient separately. Their health condition was followed up after discharge from the hospital for a period of two years through phone calls or visits to the neurology clinic. The outcomes during the follow-up period were recorded in the checklist. The outcome of the patients was classified into three groups: complete recovery, partial recovery with neurological complications and death.

2.6. Ethical considerations

All patient information remained strictly confidential, and informed consent was obtained from the parents of all participants before they were enrolled in the study. This study received approval from the ethics committee of Tehran University of Medical Sciences, and was assigned the ethics code IR.TUMS.MEDICINE.REC.1397.973.

2.7. Statistical analysis

The data were analyzed using SPSS version 26 software, with the normality of quantitative data distribution assessed using the Kolmogorov-Smirnov test. Descriptive statistics, including mean and standard deviation for quantitative variables, and frequency and relative frequency for qualitative variables, were used to report the descriptive data.

3. Results

All patients hospitalized with hypotonia in the PICU of these hospitals, during a time period of 2 years were included in the study. (n=65) Among all 65 children enrolled in the study, approximately 63% were boys, with a boys-to-girls population ratio of 1.7 to 1. The mean age of these patients was 18 months, ranging from 3 months to 15 years. Half of the children were younger than two years of age. The most common cause of hypotonia was lower motor neuron (LMN) involvement with spinal muscular atrophy (SMA) disease, while syndromic causes were the most common for upper motor neuron (UMN) involvement. The demographic characteristics of these patients are summarized in table 1.

The pediatric neurologist selected appropriate paraclinical measures based on the findings of the history and clinical examination. Neuroimaging was performed for 25 children, out of which 15 showed pathological findings. 31 children underwent EMG/NCV examination, and abnormalities were detected in 25 cases. Metabolic studies were conducted in 14 children, with only one patient reporting abnormal findings. Genetic testing was performed for 32 children, revealing abnormalities in 28 cases. All nine lumbar punctures (LP) performed yielded normal results. Among the 11 cases that underwent echocardiography, evidence of cardiomyopathy was present in 7 patients. Muscle biopsies were performed in 3 children, all of which showed abnormalities. However, twenty percent of the patients had an unknown etiology without a specific underlying cause for hypotonia. The most common underlying causes were spinal muscular atrophy (SMA) (16.9%) and Guillain-Barre syndrome (13.8%). Table 2 provides detailed information on the anatomical involvement mentioned above. Out of all 65 examined chil-

Table 1 Demographic and clinical characteristics of the children with hypotonia

Variables		Number (Percentage)
Gender	Male	41 (63.1)
	Female	24 (36.9)
Anatomic involvement	LMN	29 (43)
	UMN	25 (31)
	LMN+UMN	4 (6)
	Unknown	13 (20)
Family history	Positive	17 (26.2)
	Negative	48 (73.8)
Abnormal craniofacial features	Positive	14 (21.5)
	Negative	51 (78.5)
Hepatosplenomegaly	Positive	0 (0.0)
	Negative	60 (100)

LMN: Lower motor neuron; UMN: Upper motor neuron

Table 2 Classification of anatomical involvement and underlying causes of hypotonia

Anatomical involvement	Causes	Number
LMN	Anterior horn cells of the spinal cord (SMA)	11
(n=28)	Neuropathy (GBS, CIDP)	10
	Neuromuscular junction (MG, botulism)	4
	Muscle (myopathy)	3
UMN	Inflammatory (ADEM, ANEC)	2
(n=20)	Structural (Joubert, Aicardi, CP, Kleefstra)	7
	Syndromic (Down, Pradervili, Engelman, Smith- Lemli-Opitz)	8
	Metabolic (MMA, Pompe)	3
Both (UMN and LMN)	Mitocondrial	2
(n=4)	Warburg	1
	Trauma	1
Unknown (n=13)		13

LMN: Lower motor neuron; UMN: Upper motor neuron; SMA: Spinal muscular atrophy; GBS: Guillain-Barré syndrome; CIDP: Chronic inflammatory demyelinating polyradiculoneuropathy; MG: Myasthenia gravis; MMA: Methylmalonic acidemia ANEC: Acute necrotizing encephalopathy of childhood; ADEM: Acute disseminated encephalomyelitis; CP: Cerebral palsy

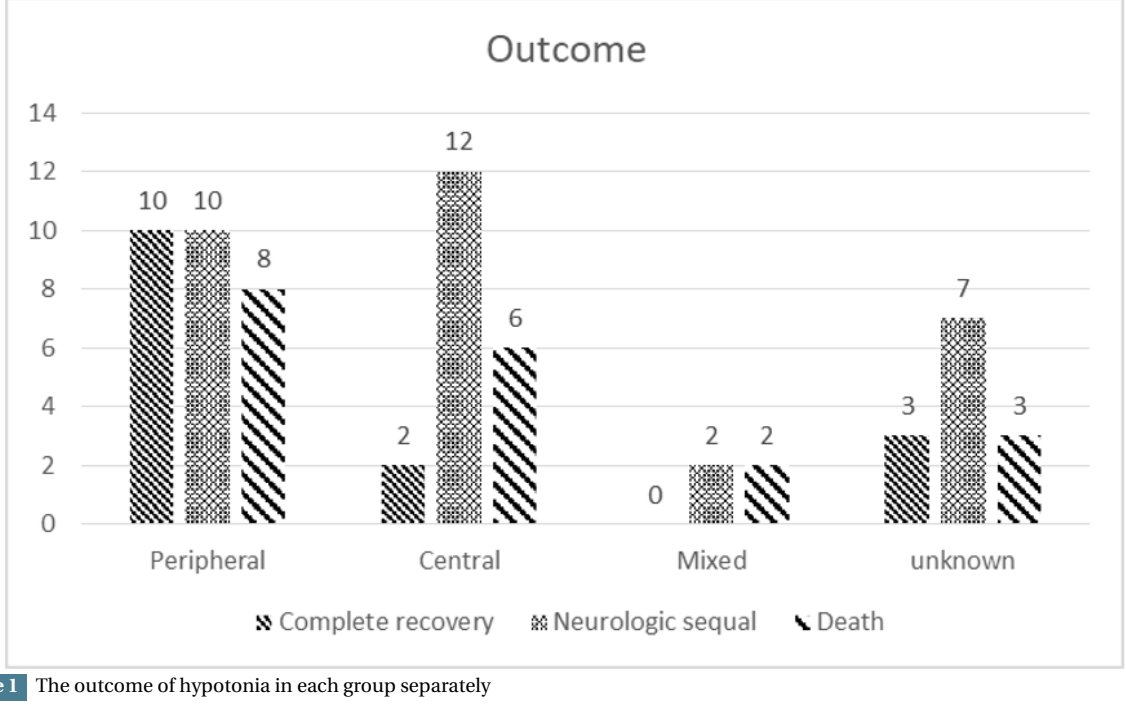

Figure 1 The outcome of hypotonia in each group separately

dren, 15 (23.1%) fully recovered, 31 (47.7%) experienced neurological sequelae, and 19 (29.2%) passed away. The neurological sequelae included delays or failure to acquire developmental skills, behavioral disorders, and seizures. The mortality rate among children with hypotonia was 29.2%, with respective proportions of 42% related to peripheral causes, 31.5% to central causes, 10.5% to combined central and peripheral causes, and 15.7% to unknown causes. There was no significant relationship found between gender, age, family history, and underlying causes (P-values: 0.235, 0.684, 0.658 respectively). However, there was a statistically significant relationship observed between neuroimaging and EMG/NCV findings and underlying causes (P-value=0.000). On the other hand, no statistically significant relationship was found between metabolic studies and underlying causes (X^2=0.09, P-value=8.907). Genetic testing revealed a statistically significant relationship with underlying causes, with most affected cases related to peripheral causes (X^2=17.079, P-value=0.002). Lumbar punctures (LP) were performed in 9 cases, all yielding normal results. Both muscle biopsies performed were abnormal and due to peripheral causes. However, there was no statistically significant relationship between underlying cause and disease outcome (X^2=6.695, P-value=0.369).

4. Discussion

Hypotonia in infants and children presents a common and significant challenge, encompassing a broad range of potential diagnoses. Severe cases requiring hospitalization in the ICU pose a particularly serious diagnostic and therapeutic challenge for physicians. Given the potentially life-threatening nature of these cases, accurate diagnosis and prompt treatment are crucial. An essential aspect of classifying hypotonia is distinguishing between central and peripheral involvement, which aids physicians in selecting appropriate diagnostic and treatment strategies (2,8).

Our study included 65 patients, who were categorized according to their prevailing nervous system disability into peripheral (43.7%), central (20.76%), and combined (6.17%) groups. Unknown causes were identified in 20% of cases. SMA and Guillain-Barre syndrome were the most common diseases observed. Regarding short-term outcomes (at discharge from the hospital), 23.1% (15 patients) fully recovered, while 29.2% (19 patients) unfortunately passed away. However, our long-term follow up (2 years after discharge) showed that 47.7% (31 patients) experienced neurological complications.

A study by Fathalla Gad et al. is the most similar available study in terms of the studied population. Their study, conducted on 32 children with peripheral hypotonia, reported that more than half of the patients were diagnosed with Guillain-Barre syndrome (18 patients, 56.3%), while the remaining cases included Duchenne dystrophy, SMA, and myositis, respectively (9). Similarly, the results of our study revealed that out of 28 children with peripheral hypotonia, diagnoses included SMA, Guillain-Barre syndrome, myasthenia gravis, botulism, and myopathy.

Among the limited number of studies conducted on patients admitted to the intensive care unit (ICU), we can refer to a study by Sarikaya et al., where all patients admitted to this department over an 11-year period were examined, revealing that only 3% of them had neuromuscular involvement, including genetic, metabolic, and acquired causes (10). In another study by Harrar et al., a retrospective review of patients hospitalized in the PICU over an 11-year period identified 24 cases of neuromuscular diseases, with the most common being Guillain-Barre syndrome and myasthenia gravis (8). It is worth noting that these studies examined all patients hospitalized in the PICU, whereas in our study, we focused specifically on children with hypotonia admitted to the PICU.

A study by Eng GD revealed that 85% of hypotonia cases in children were caused by central factors, with the remaining 15% attributed to peripheral causes. Among central hypotonia cases, cerebral palsy accounted for 88%, while spinal cord anterior horn cell diseases and muscle diseases were the predominant causes of peripheral hypotonia, at 51% and 31% respectively (11). Conversely, a study by Paine et al. focused on infants with hypotonia and developmental disorders in outpatient settings, where 80% of cases had central causes, predominantly cerebral palsy (12). These results differ from our findings, possibly due to variations in the study populations. Unlike our hospitalized patients in the PICU, both studies were conducted on outpatients.

Biridi et al. studied children with hypotonia over a 10-year period and reported that the diagnosis remained unknown in approximately one-third of patients. Regarding the final outcome, 8 infants passed away before their first birthday, while 30 cases experienced complete recovery without complications, and 38 had developmental delays (3). These findings are inconsistent with our results, particularly the mortality rate of 29.2% among children with hypotonia. This difference can be attributed to the severity of the patients' condition hospitalized in the PICU. In a study by Sarikaya, approximately 7% mortality was reported among neuromuscular patients (10), whereas approximately 28% of patients with peripheral involvement died in our study.

Biridi et al. emphasized the importance of electrophysiological testing, which, when combined with muscle biopsy, can provide valuable diagnostic information (3). Similarly, in our study, a statistically significant relationship was observed between the results of EMG-NCV findings and underlying causes of hypotonia. This finding may be influenced by the larger number of patients with peripheral hypotonia in our study.

In our study, a statistically significant relationship was found between the findings of neuroimaging and genetic tests with the underlying causes of hypotonia. Specifically, most cases with impaired neuroimaging were associated with central causes, while most cases with impaired genetic tests were associated with peripheral causes (3,13).

5. Conclusion

Identifying the underlying causes of hypotonia in patients hospitalized in the ICU is crucial. It aids physicians in promptly diagnosing the condition and implementing suitable treatment strategies, thereby averting the complications associated with delayed diagnosis.

6. Strengths and limitations

Given that our study focuses on critically ill patients admitted to the ICU, it represents one of the few investigations conducted in this domain. Many of the previous studies were conducted in outpatient settings and clinics.

It is important to note that our findings are specific to specialized referral centers and patients hospitalized in the intensive care unit and may not be generalizable to all hypotonic patients. Additionally, limitations such as retrospective data collection and incomplete in the patients' medical records should be considered when interpreting our results.

7. Declarations

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7.2. Authors' contribution

The authors meet all criteria for authorship based on the recommendations of the International Committee of Medical Journal Editors (ICMJE).

7.3. Conflict of interest

The authors declare no conflict of interest.

7.4. Funding

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