늘어지는 영아 증후군의 진단적 분류와 발달 예후: 단일 3차 병원에서의 연구

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Etiological Classification and Developmental Outcomes in Floppy Infants: A Single Tertiary Center Experience

Purpose: Floppy infants or congenital hypotonia indicates decreased muscle tone in infants secondary to abnormalities of the central or the peripheral nervous system, or both. Previous literature classified its causes as those attributable to a central vs. peripheral origin; however, recent studies have introduced a newer classification describing a combined origin. We investigated floppy infants by applying the new etiological classification and reviewed the most common etiologies based on the age of presentation. We additionally reviewed the clinical characteristics, diagnoses, and the developmental outcomes in these infants.

Methods: We retrospectively reviewed the electronic medical charts and recruited 116 infants diagnosed with floppy infant syndrome between January 2005 and December 2016 at Severance Children's Hospital. Among these infants, 66 with a confirmed diagnosis were reviewed for the etiological classification. Information regarding developmental outcomes was obtained via phone interviews with the infants' families.

Results: Based on the new etiological classification, among 69 infants with a confirmed diagnosis, in 40 (34.5%) this syndrome was of central origin, in 19 (16.4%) of peripheral origin, and in 10 (8.6%) of combined origin. Prader-Willi syndrome, myotonic dystrophy, and spinal muscular atrophy were the most common disorders observed and combined hypotonia showed the poorest developmental outcome.

Conclusion: The study states the importance of proper evaluation of etiological diagnosis and optimal intervention for developmental prognosis. The introduction of a new etiological group of combined hypotonia especially emphasizes regular monitoring and timely rehabilitative intervention in patients for the better quality of life in them as well as their caregivers.

Key Words: Decreased muscle tone, Hypotonia, Prader-Willi syndrome, Myotonic dystrophy, Spinal muscular atrophy

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Introduction

Hypotonia is a condition characterized by diminished tone of skeletal muscles with decreased resistance of muscles to passive stretching. It can be caused by

abnormalities of the central nervous system (CNS) or of the lower motor neurons (LMN), or both¹⁾. Pediatric neurologists ought to evaluate whether a hypotonic child is only hypotonic or shows hypotonia and concomitant weakness. They should ascertain whether those with floppy infant syndrome (who show decreased tone) additionally present with delayed acquisition of psychomotor developmental milestones, and if they do, whether such delay is an exclusive motor delay or a motor and concomitant cognitive delay²⁾. Detailed history taking and physical examination constitutes the first step by which clinicians determine whether the condition is of central or peripheral origin. Accurate diagnosis is essential to guide the interventional approach and to inform a patient's parents regarding prognosis and genetic counseling^{3,4)}.

Current studies have classified floppy infant syndrome based on its etiological diagnosis and described the clinical manifestations, diagnostic algorithms, and newly developed genetic diagnostic tools including next-generation sequencing (NGS). Dubowitz et al. subclassified the primary classification into 2 broad categories—paralytic and non-paralytic conditions⁵⁾. Bodensteiner categorized congenital hypotonia into central and motor unit hypotonia²⁾. Jain et al. described conditions associated with central (non-paralytic) hypotonia and paralytic/neuromuscular hypotonia³⁾. Prasad et al. categorized this condition into central hypotonia associated with normal brain and myelination, CNS malformations, genetic and chromosomal disorders, motor unit hypotonia, and metabolic disorders⁶⁾. Most studies have classified floppy infant syndrome into central or peripheral etiologies. Central hypotonia suggests the presence of encephalopathy (altered consciousness/seizures) or global developmental delay with lack of muscle weakness. Peripheral hypotonia indicates skeletal muscle weakness associated with an inability to move the extremities against gravity, with or without elevated serum creatine kinase levels. However, central and peripheral hypotonia may coexist in a few infants. For example, those with mitochondrial disorders, Fukuyama-type congenital muscular dystrophy, and perinatal asphyxia secondary to motor unit disease demonstrate cognitive impairment or encephalopathy with LMN weakness. Thus, Emily et al. classified the etiology of floppy infant syndrome into central, peripheral, and combined hypotonia⁷⁾. Introduction of the concept of combined hypotonia has helped in determining developmental outcomes of diseases affecting both, the central and the peripheral organs.

Based on the diagnostic approach to hypotonia introduced by Emily et al. we classified infants with floppy infant syndrome into 3 etiological classes—central, peripheral, and combined hypotonia for optimal decision-making and treatment appro-

aches. There is no precedent domestic research regarding floppy infants classified into three etiology groups. We reviewed the clinical characteristics and diagnosis and evaluated differences in the diagnosis depending upon the age of presentation. Furthermore, we compared the developmental prognosis of each group.

Materials and Methods

We reviewed electronic medical records and performed a retrospective study in infants with congenital hypotonia who presented to the Severance Children's Hospital between March 2005 and May 2017. A total of 200 patients between the ages of 0 and 18 whose diagnosis was clinically confirmed by the attending pediatricians or pediatric neurologist following history taking and physical examination were recruited. Among the 200 patients with hypotonia, 84 were eliminated for insufficient information due to fewer than twice number of clinic visits. Finally, 116 patients confirmed with congenital hypotonia were included in the study. We reviewed medical information including sex, age of presentation, duration of follow-up, prenatal, perinatal, and postnatal history and associated symptoms (poor sucking/crying, dysmorphic facial features, and/or seizures). Neuroradiological and biochemical investigations (lactate:pyruvate ratio [L:P ratio], serum creatine kinase levels), electromyography, nerve conduction velocities, and chromosomal/genetic analysis were performed to establish an etiological diagnosis of hypotonia. Etiologies were categorized into central, peripheral, and combined etiologies according to the involved organs. The presence of encephalopathy with lack of muscle weakness was categorized as central, low motor neuron weakness without CNS involvement was categorized as peripheral and cognitive impairment or encephalopathy with LMN weakness was categorized as combined hypotonia. Previous diagnostic evaluations were reviewed in those who were undiagnosed, and they were classified into probable etiological groups based on their clinical manifestations.

Furthermore, to establish a quick first impression for infants with floppy infant syndrome based on the age of onset, we investigated the frequency of diagnoses based on the age of presentation as <1 month, 1 month–1 year, and >1 year.

Information regarding the developmental outcomes related to each domain (respiration, feeding, language, cognition, and motor function) was obtained via phone interviews of the infants' parents, and we investigated developmental outcomes in the 3 etiological groups.

The study was approved by the Institutional Review Board of

the Yonsei University Health System (IRB number: 2018-2141-001).

Results

1. Demographic data

The 116 patients investigated included 51 (44%) male infants and 65 (56%) female infants. We observed that 35 infants (30.2%) presented first symptoms before the age of 1 month, 58 (49.9%) at age 1–12 months, and 23 (19.8%) at >1 year of age. The mean age at the time of presentation of symptoms was 10.7 ± 18.3 months. The mean age at the last visit was 39.0 ± 39.8 months and the duration of follow up was 28.4 ± 35.7 months.

2. Clinical characteristics

Birth and perinatal/postnatal history are summarized in Table 1. In the context of birth history and presenting symptoms, a family history of peripheral hypotonia was discovered in 3 infants (33%, all patients with myotonic dystrophy [MD]) and none for the central group. In the context of prenatal history, the number of infants with polyhydramnios was higher in the peripheral than in the central hypotonia group (7 [77.8%] vs. 3 [15.8%]). In the context of postnatal history, the number of infants with respiratory distress was higher in the peripheral than in the central hy-

potonia group (8 [88.9%] vs. 8 [42.1%]). Correspondingly, the rate of intubation in the delivery room was higher in the peripheral than in the central hypotonia group (6 [66.7%] vs. 5 [26.3%]); however, the rate of application of the neonatal resuscitation protocol was similar between groups. Associated symptoms such as dysmorphic facial features and seizures, which indicate the occurrence of chromosomal anomalies were more common in the central than in the peripheral hypotonia group (5 [26.3%] vs. 1 [11.1%]). Notably, >50% of the infants in both groups demonstrated poor sucking or crying: 12 (63.1%) in the central and 9 (100.0%) in the peripheral group.

3. Diagnosis

Among the 116 hypotonic infants investigated, etiological diagnosis was confirmed in 69 (59.5%). Among these 69, 40 (34.5%) were classified as showing central, 19 (16.4%) as peripheral, and 10 (8.6%) as combined hypotonia. Among the 35 infants with floppy infant syndrome who were symptomatic before the age of 1 month, diagnosis was confirmed in 23 (65.7%): 12 (34.3%) showed central, 8 (22.9%) showed peripheral, and 3 (8.6%) showed combined hypotonia.

1) Established etiological diagnoses

The distribution of diseases in each group is presented in Table 2. Central hypotonia was identified in 40 infants (34.5%). Prader-

Table 1. Birth History and Presenting Symptoms (N=31)

	Central hypotonia N=19 (%)	Peripheral hypotonia N=9 (%)	Combined hypotonia N=3 (%)
Family history			
Affected family member(s)	0 (0.0)	3* (33.3)	
Prenatal history			
Decreased fetal movements	2 (10.5)	4 (44.4)	
Intra-uterine growth restriction	6 (31.6)	0 (0.0)	1 (33.3)
Polyhydramnios	3 (15.8)	7 (77.8)	1 (33.3)
Perinatal history	2 (10.5)	4 (44.4)	
Breech presentation			
C-section	14 (73.7)	7 (77.8)	
Postnatal history	2 (10.5)	4 (44.4)	
Apgar between 1–3 at 1, 5 min			
Birth weight (kg)	2.76 ± 0.49	2.35 ± 0.63	2.92
Intubation in delivery room	5 (26.3)	6 (66.7)	1 (33.3)
Meconium aspiration	2 (10.5)	0 (0.0)	1 (33.3)
Respiratory distress	8 (42.1)	8 (88.9)	2 (66.7)
Resuscitation	1 (5.3)	1 (11.1)	
Other presenting symptoms	5 (26.3)	1 (11.1)	
Dysmorphic face			
Poor sucking/weak cry	12 (63.1)	9 (100.0)	
Seizure	3 (15.8)	0 (0.0)	3 (100.0)

*Three of them were congenital myotonic dystrophy.

Table 2. Established Etiologic Diagnoses in 69 Floppy Infants

Category	All N=69 (%)	Neonate N=23 (%)
Central hypotonia (N=40)		
Brain malformation	4 (5.8)	
Intractable epileptic encephalopathy	5 (7.2)	2 (8.7)
HIE/Cerebral palsy	5 (7.2)	
Tethered cord syndrome	3 (4.3)	
Prader-Willi/Angelman syndrome	16 (23.2)	7 (30.4)
MECP2 spectrum disorder	1 (1.4)	
Zellweger syndrome	1 (1.4)	1 (4.3)
Other chromosome abnormalities	5 (7.2)	2 (8.7)
Peripheral hypotonia (N=19)		
Spinal muscular atrophy	7 (10.1)	
Congenital myotonic dystrophy	7 (10.1)	5 (21.7)
Congenital myopathy/congenital muscular dystrophy	2 (2.9)	1 (4.3)
Charcot-Marie-Tooth disease	1 (1.4)	1 (4.3)
Arthrogryposis multiplex congenita	2 (2.9)	1 (4.3)
Combined hypotonia (N=10)		
Mitochondrial myopathy	4 (5.8)	2 (8.7)
Fukuyama type congenital muscular dystrophy	1 (1.4)	
PDHA1 deficiency	2 (2.9)	1 (4.3)
Menkes' disease	2 (2.9)	
Tay-sachs disease	1 (1.4)	

HIE, hypoxic ischemic encephalopathy; MECP2, Methyl-CpG-binding protein 2; PDHA1, pyruvate dehydrogenase alpha.

Willi (PWS)/Angelman syndrome (diagnosed in 16 infants [23.2%]) was the most common disorder among all hypotonia groups. The highest percentage of infants in the peripheral hypotonia group belonged to the spinal muscular atrophy (SMA) and the MD categories—each subgroup included 7 infants (10.1%). The highest percentage of patients in the combined hypotonia group belonged to the mitochondrial encephalomyopathy subgroup (4, 5.8%).

2) Etiological diagnosis based on the age of presentation

The etiological diagnostic rate based on the age of presentation is summarized in Table 3. The age of presentation is classified into three categories: neonates (<1 month), 1–12 months and 1–5 years. Infants were diagnosed with floppy neonates if hypotonia was first identified before 1 month of life. We observed 7 infants (29.2%) with PWS and 5 (20.8%) with MD. PWS and MD were most commonly identified among those diagnosed with floppy infant syndrome. In addition to these PWS and MD, other conditions observed included 2 infants (8.3%) with early infantile epileptic encephalopathy (EIEE) and 2 (8.3%) with mitochondrial myopathy. Among the 2 with mitochondrial myopathy, the serum L:P ratio was increased during the neonatal period, which was later confirmed using a muscle biopsy. SMA was the most common disease (6, 17.6%) among infants aged 1–12 months. In this study, 6 of 7 patients with SMA developed symptoms during infancy, although no infant was diagnosed during the neonatal period. PWS was consistently observed among a high percentage of infants in the group (6, 17.6%), followed by the occurrence of brain malformations (4 infants, 11.8%). The infants aged 1–5 years accounted for the least number of infants with floppy infant syndrome 2 (18.2%) with PWS, 2 (18.2%) with Menkes disease, and 2 (18.2%) with cerebral palsy.

3) Infants without a confirmed diagnosis of floppy infant syndrome

Patients without diagnostic confirmation were classified into a 'probable disease group' based on their clinical characteristics (Table 4). The percentage of patients with a high index of suspicion for central hypotonia was the highest in this group. We ob-

served 8 patients (17.0%) with mild abnormalities in brain imaging, 5 (10.6%) with idiopathic focal or generalized epilepsy, 7 (14.9%) who were awaiting the results of NGS or other genetic tests based on a stepwise approach, and 10 (21.3%) with global developmental delay with no apparent diagnostic abnormalities. A few patients with a high index of suspicion for peripheral hypotonia were also evaluated without muscle biopsy confirmation, and a few others showed generalized hypotonia with relatively normal cognition and no apparent diagnostic abnormalities.

4. Prognosis

We investigated developmental outcomes in those with floppy infant syndrome via a phone interview with the parents of 116 infants diagnosed with this condition. Information regarding developmental outcomes was classified and assessed under 5 sections (respiration, feeding, language, cognition, and motor function). Among the 116 infants evaluated, 7 (6.4%) had died of disease including early infantile epileptic encephalopathy, agyria-pachygyria complex, Zellweger syndrome, Charcot-Marie-Tooth disease with severe hypoxic ischemic damage, Tay-Sachs disease, and 2 other undiagnosed conditions (1 patient expired after discharge from the neonatal intensive care unit [NICU]). We could interview parents of only 102 infants because 7 parents did not answer or had their contact information changed. The mean age

Table 4. 47 Floppy Infants without Confirmative Diagnosis

Category	All N=47 (%)	Neonate N=8 (%)
Central hypotonia	8 (17.0)	1 (1.3)
Mild abnormality in brain imaging		
Partial or generalized epilepsy	5 (10.6)	1 (1.3)
r/o genetic/chromosomal disease	7 (14.9)	3 (3.8)
Global developmental delay with no apparent abnormal diagnostic findings	10 (21.3)	
Peripheral hypotonia		
r/o muscle disease without muscle biopsy confirmation	4 (8.5)	1 (1.3)
Combined hypotonia		
r/o metabolic disease	3 (6.4)	2 (2.6)
Generalized hypotonia with relatively normal cognition and no apparent abnormal diagnostic findings	7 (14.9)	
Unknown (follow up loss)	3 (6.4)	

Table 3. Etiologic Diagnosis in 69 Floppy Infants According to the Patient's Age of Presentation (Total N=69)

	Neonates (<1 month) N=24 (%)	1–12 months N=34 (%)	1 year–5 years N=11 (%)
Most common	Prader-Willi syndrome 7 (29.2)	Spinal muscular atrophy 6 (17.6)	Prader-Willi syndrome 2 (18.2)
2 nd most common	Myotonic dystrophy 5 (20.8)	Prader-Willi syndrome 6 (17.6)	Menkes disease 2 (18.2)
3 rd most common	Early infantile epileptic encephalopathy 2 (8.3)	Brain malformation 4 (11.8)	Cerebral palsy 2 (18.2)
	Other chromosome anomalies (down syndrome) 2 (8.3)	Intractable epileptic encephalopathy 3 (8.8)	Tethered cord syndrome 1 (9.1)
	Mitochondrial myopathy 2 (8.3)	Myotonic dystrophy 2 (5.9)	Cri du chat syndrome 1 (9.1)
		Mitochondrial myopathy 2 (5.9)	Rett's syndrome 1 (9.1)
		Congenital myopathy 1 (2.9)	

at phone interview was 37.0 ± 22.0 months. Among 102 infants whose parents were interviewed, 12 (11.8%) were able to ambulate independently and 19 (18.6%) were bed-ridden. We observed that 25 (24.5%) and 22 infants (21.6%), respectively showed normal cognitive function and intact language ability. We observed that 8 infants (7.8%) required home ventilator support with tracheostomy and 9 (8.8%) required gastrostomy and percutaneous endoscopic gastrostomy (PEG) tube placement (Table 5).

Developmental outcomes in the different hypotonia groups were compared with respect to these 5 categories, each of which had 3 or 4 answers that could be chosen based on the infants' activities. In terms of feeding and respiration, the number of patients requiring gastrostomy and tracheostomy was the highest in the combined and lowest in the central hypotonia group. The maximal developmental achievement in physical, language and cognitive development was observed in the central hypotonia and minimal achievement (poorest outcomes) in the combined

hypotonia group. For example, 89% of infants in the combined hypotonia group were unable to communicate properly and 66% of these could not speak a word (Fig. 1–5).

Discussion

The overall diagnostic rate observed in our study is fairly consistent with previous literature. We investigated 116 infants, and etiological diagnosis was confirmed in 69 (59.5%). A retrospective study of infants with floppy infant syndrome performed between 1990 and 2000 by Birdi et al. established a definitive diagnosis in 60 of 89 infants (67.4%) [4,8]. Sul et al. confirmed the etiological diagnosis in 80 (62.5%) of 128 infants studied between 2008 and 2012⁹⁾. The difference between these studies is that Birdi et al. included 9 infants with benign hypotonia (10.1%) in their definitive diagnosis. In our study, 7 infants (6.0%) with generalized hypotonia with relatively normal cognition who could be diagnosed

Table 5. Current Clinical Outcome of 116 Floppy Infants

Total N=116 (%)		
Mortality	Survived	109 (94.0)
	Expired	7 (6.4)
Motor function	Bed-ridden	19 (18.6)
	Wheel chair bound	71 (69.6)
	Ambulatory	12 (11.8)
Cognitive development	No communications	47 (46.1)
	Communicable	30 (29.4)
Language	Normal	25 (24.5)
	No word	39 (38.2)
	Few words, sentences	41 (40.2)
	Normal	22 (21.6)
Respiratory support	Home ventilator	8 (7.8)
Feeding	Gastrostomy and PEG	9 (8.8)

PEG, percutaneous endoscopic gastrostomy.

Fig. 1. According to respiration, the number of patients with no need for oxygen support is highest in central hypotonia group.

Fig. 2. According to feeding, the number of patients without need for support is highest in the central hypotonia group.

Fig. 3. According to motor function, the number of bedridden patients is highest in combined hypotonia group.

with benign hypotonia at the end of the follow-up period were excluded from the definitive diagnosis. In our study, the 3 most common diagnoses included PWS (23.2%), SMA (10.1%), and MD (10.1%), all of which were diagnosed using molecular genetics. Sul et al. demonstrated that PWS (21.3%), SMA (7.5%), hypoxic ischemic encephalopathy (HIE) (7.5%), and MD (5.0%) were the most commonly diagnosed conditions. However, the study reported by Birdi et al. reported that the 3 most common disorders were HIE (8.3%), PWS (8.3%), and agenesis of the corpus callosum (6.7%), and the diagnosis could be confirmed in a relatively small percentage of patients with MD (3.3%) and SMA (3.3%). The percentage of infants in our study in whom diagnosis could be confirmed using molecular genetics (72.4%) correlates with the study reported by Sul et al (71.3%). However, Birdi et al. reported a much lower percentage of diseases that were confirmed using molecular genetics (15.0%). Molecular diagnostics and genetic testing are widely utilized and have simplified diagnostic processes. Thus, the percentage of infants in whom etiological diagnosis can be confirmed via genetic diagnostic tools has greatly improved

in recent studies.

Our results assessed the occurrence of different disorders based on the age of onset. Among infants with floppy infant syndrome, PWS (29.2%), MD (20.8%), and EIEE (8.3%) were the most common diagnoses. Lawrence et al. performed an 11-year retrospective cohort study to investigate infants with floppy infant syndrome and observed that the etiologies most commonly identified included HIE (26%), PWS (12%), and MD (12%). Among a total of 7 infants with SMA across all age groups, 2 were diagnosed with SMA type I and in both, symptoms were recognized at the age of 3 months in our study. However, SMA type I (2.0%) in neonatal period was diagnosed in only 1 case in the study reported by Lawrence et al. and was not identified in our study. Considering the overall diagnostic rate of SMA, the low diagnostic rate is perhaps attributable to the difficulty in diagnosing infants with severe manifestations at birth and the consequent early mortality.

Infants in the peripheral hypotonia group showed a higher rate of respiratory distress at birth (8/9, 88.9%) and a higher intubation rate (6/9, 66.7%) than that in the central hypotonia group (42.1% and 26.3), respectively. Polyhydramnios and decreased fetal movements were more commonly observed in the peripheral (77.8%) than in the central hypotonia group (15.8%). MD accounted for the highest percentage of infants (7/19, 38%) in the peripheral hypotonia group, and fetuses with MD were observed to demonstrate polyhydramnios in previous studies¹⁰. The simplest explanation for the occurrence of hydramnios is a neuromuscular failure in fetal swallowing in utero. This mechanism was demonstrated by an experiment in which the injection of contrast medium into the amniotic fluid in a fetus with suspected MD showed delayed swallowing of the contrast medium¹¹.

The new approach involves a combined hypotonia group, which includes infants showing both, central and peripheral hypotonia. In our study, the highest percentage of infants with combined hypotonia were diagnosed with mitochondrial encephalomyopathy. In contrast to previous studies reported by Sul⁹ Kim¹² in which infants with mitochondrial encephalomyopathy were not included, our study demonstrated that most infants included in the combined hypotonia group were diagnosed with mitochondrial encephalomyopathy because our center specializes in diagnosing and treating mitochondrial encephalomyopathy. The prognosis of the combined hypotonia group was poorer than that related to other etiologies for developmental evaluations. Infants with combined hypotonia showed the highest rate of tracheostomy and PEG tube placement and the poorest motor and language function and cognition. Mitochondria are primarily involved with energy production, and because all organs

Fig. 4. According to cognition, the number of patients unable for communications is highest in combined hypotonia.

Fig. 5. According to language, the number of patients unable to speak a word is highest in combined hypotonia group.

including the brain, the heart, muscles and bones are dependent upon adenosine triphosphate, mitochondrial disorders affect all systems and present with heterogeneous features¹³⁾. Concurrent impairment of both, the central and peripheral organs raises the suspicion of a very poor prognosis in patients with combined hypotonia compared to other groups.

Central hypotonia demonstrated the most favorable developmental outcome in our study. No infant with PWS required a tracheostomy and gastrostomy, and 3/16 infants (18.8%) did not show impaired cognitive and/or language function. Most infants with PWS showed poor sucking and failure to thrive during infancy necessitating nasogastric or other special feeding techniques. However, a gastrostomy is rarely necessary because this condition is transient and occurs only in the early neonatal period. Physicians can determine optimal treatment strategies by predicting the prognosis in infants with floppy infant syndrome based on their diagnosis. Early diagnosis and prompt intervention guided by assessment of developmental outcomes and optimal timing of tracheostomy and gastrostomy are particularly important in those with a diagnosis of combined hypotonia or those who show characteristics of combined hypotonia. In contrast to patients with a confirmed diagnostic etiology, undiagnosed patients demonstrating generalized hypotonia with relatively normal cognition and no apparent diagnostic abnormalities rarely show developmental impairment. Most infants with congenital hypotonia with a good prognosis at the interview could be diagnosed with benign congenital hypotonia or congenital hypotonia with favorable outcomes¹⁴⁾.

Limitations of the study: 1) This study was performed at Severance Children's Hospital, which manages a significantly high percentage of patients with clinically severe disease, particularly in the NICU. Thus, the large number of patients transferred from the NICU with severe physical and cognitive dysfunction could lead to a bias in determining the mean developmental prognosis of infants with floppy infant syndrome. 2) This study was performed between 2005 and 2016 and a few infants aged only 1-2 years require longer follow-up to accurately assess further developmental outcomes.

Our study emphasizes the importance of appropriate evaluation of etiological diagnosis and optimal intervention for developmental prognosis. The introduction of a new etiological group of combined hypotonia, which is associated with poorer outcomes warrants regular monitoring and timely intervention in infants including adequate feeding and ventilator support. Motor, cognitive, and language dysfunction hinder the quality of life in patients as well as caregivers. Therefore early diagnosis and appropriate rehabilitation of infants with combined hypotonia is very important.

The same strategy is also required for the management of central and peripheral hypotonia. Further multicenter prospective studies using a standardized protocol and systematic evaluation are warranted to gain a better understanding of the diagnosis and decision-making for optimal treatment.

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요약

목적: 늘어지는 영아 증후군은 중추신경계 이상, 말초 신경계 이상 혹은 둘 모두의 이상으로 발생할 수 있다. 늘어지는 영아에서 원인을 진단하는 것은 환자의 치료와 발달 예후를 결정하는 중요한 요소로 현재까지 다양한 진단 알고리즘이 제안되고 있다. 본 논문에서는 늘어지는 영아 증후군의 원인에 대한 새로운 분류 및 증상 발현 시기에 따른 원인, 그리고 이들의 발달 예후에 대해 연구하였다.

방법: 2005년부터 2016년까지 세브란스병원에 내원한 늘어지는 영아들을 대상으로 EMR 차트를 후향적으로 분석하여 진단 및 임상적 특징을 분석하였고 환자들의 발달에 대해 보호자에게 일대일 전화 인터뷰를 통해 조사하였다.

결과: 전체 116명의 환자 중에 원인에 대한 확진을 받은 경우가 69명으로 전체 진단율이 59.5%이었고 이들 중 Prader-Willi syndrome, myotonic dystrophy, spinal muscular atrophy가 가장 흔한 진단이었다. 전 연령대에 걸쳐 Prader-willi syndrome이 가장 흔한 진단이었고 특히 1개월 미만 증상 발현군에서는 Prader-willi syndrome, myotonic dystrophy, early infantile epileptic encephalopathy가 흔한 3가지의 진단이었다. 발달 예후 면에서 원인군 중 combined hypotonia에서 전 영역에 걸쳐 가장 나쁜 예후를 보였다.

결론: 현재까지의 논문과 본 논문에서의 늘어지는 영아 증후군에 대한 진단율은 유사했고 각 연령에 따른 흔한 진단에 대해서도 알아 보았다. 발달 예후가 가장 나쁜 combined hypotonia군에 속하는 진단으로 확진되거나 의심되는 경우 초기 진단시부터 발달에 대해 체계적이고 단계적인 추적관찰이 필요하다.

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