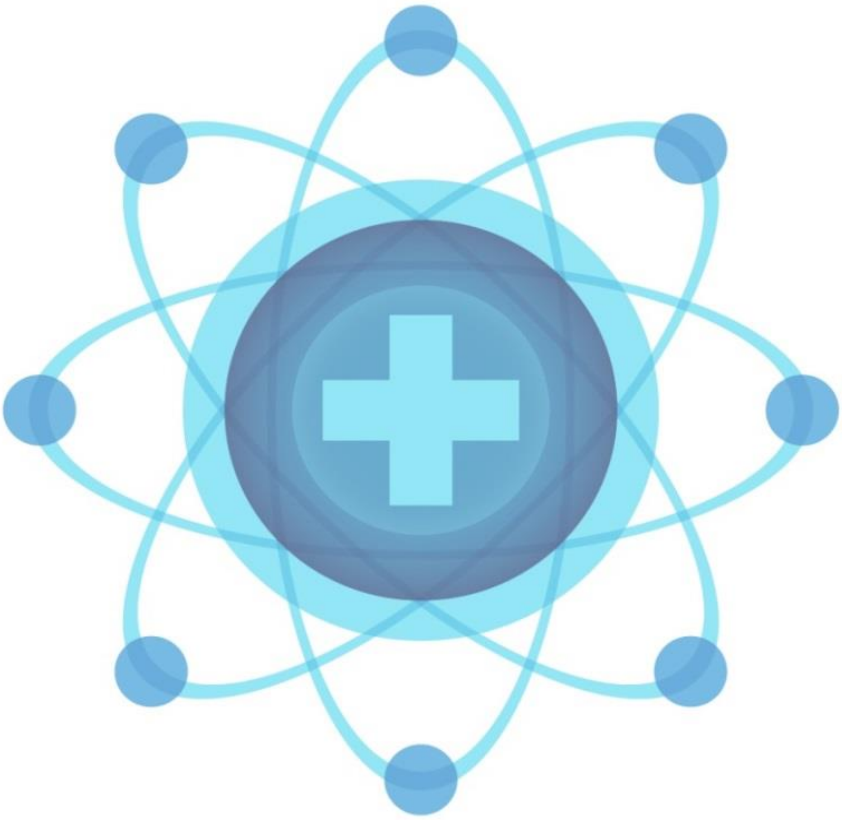

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CLINICAL AND NEUROLOGICAL CHARACTERISTICS OF HEREDITARY SPASTIC PARAPLEGIA IN A COMPARATIVE ASPECT WITH CEREBRAL PALSY

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Abstract Hereditary spastic paraplegia (HSP) most often "masks" as spastic diplegia with cerebral palsy (CP), so it is difficult to differentiate them from cerebral palsy. The aim of the study is to identify the clinical and anamnestic features of NSP in a comparative aspect with cerebral palsy, spastic diplegia. In patients with NSP, movement disorders appear later by the age of 3 years and slowly progress thereafter. Already at the age of 10-12 years, patients are forced to use auxiliary means of transportation. And with cerebral palsy of spastic diplegia, compared with NSP, from birth, the clinical picture is characterized by a lag in psychomotor development and a non-progressive course. In case of clinical verification of NSP disease, it is necessary to conduct confirmatory molecular genetic diagnostics.

Keywords: heredity, spastic paraplegia, cerebral palsy, genealogy, clinic.

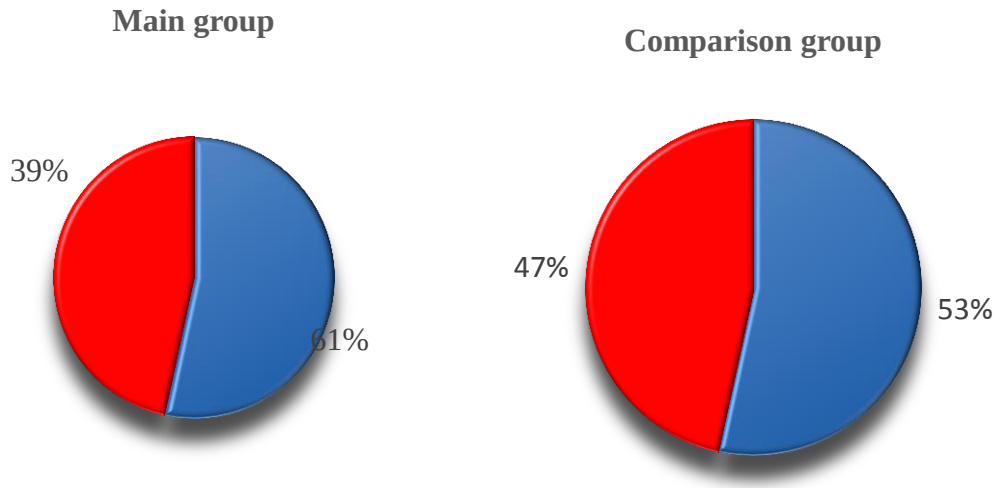
Relevance: Data on the prevalence of hereditary spastic paraplegia (HSP) vary between studies, but in general it is considered to be 3.8:100,000 in the general population (1.95:100,000 for dominant forms and 1.88:100,000 for recessive) [3,4,6,7]. It is believed that autosomal dominant spastic paraplegia is more common than autosomal recessive (55% versus 45% of the total number of patients with spastic paraplegia). Molecular genetic diagnosis is possible, but generally meaningful for SPG 3A, SPG 4, SPG 6, which together represent 60% of all autosomal dominant cases. Among the autosomal recessive forms, SPG 5 and SPG 7 are the most common [2,1,5,9]. NSP is most often "disguised" as spastic diplegia with cerebral palsy (ICP), so it is difficult to differentiate them from cerebral palsy [8,9,11]. NSP is differentiated from cerebral palsy by a form of spastic diplegia, congenital hip dysplasia, vitamin D - resistant rickets, motosensory neuropathy, polymyositis and dermatomyositis, metabolic and endocrine myopathies [3,8,10]. Taking into account the absence, to date, of pathogenetic methods for the treatment of most forms of hereditary diseases of the nervous system, the most effective method of combating these diseases is medical genetic counseling and prevention of recurrent cases of the disease in burdened families.

Research of hereditary diseases of the nervous system in various regions is of particular relevance for practical, neurological and medical genetic services.

The purpose of the study: to identify the clinical and anamnestic features of NSP in a comparative aspect with cerebral palsy, spastic diplegia.

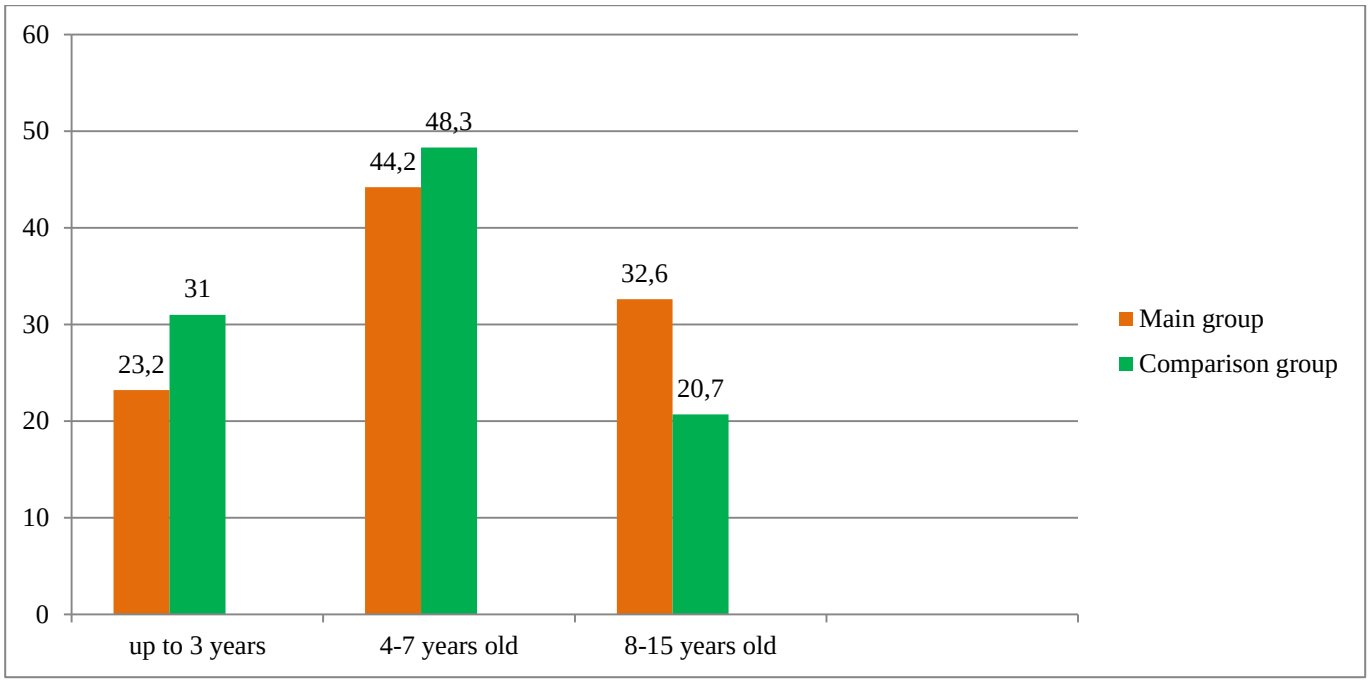
Material and methods of research: We examined 153 children. Of these, the main group consisted of 95 patients with NSP. The retrospective study included 40 children who applied to the department of medical genetic counseling of the Republican Center "Screening of mother and child" (Tashkent) for the period 2007-2017. A prospective study was conducted among 55 patients who applied in the period from 2018-2022. Patients in the amount of 58 children made up a comparison group with a diagnosis of cerebral palsy with spastic diplegia, who applied to the clinic of the Republican Psychoneurological Hospital named after. W.K. Kurbanov in the period from 2019-2022. A thorough genealogical analysis was carried out, clinical and neurological studies were used, assessment scales were used (motor activity was assessed using the MRC scale, spasticity was assessed using the Ashworth scale , gross motor functions were assessed using the GMFSC).

Results of the study: Among the examined patients of the main group, there were 58 (61%) boys and 37 (39%) girls. In the comparison group, there were 31 (53.4%) boys and 27 (46.6%) girls. Boys predominated in both groups (Fig. 1).



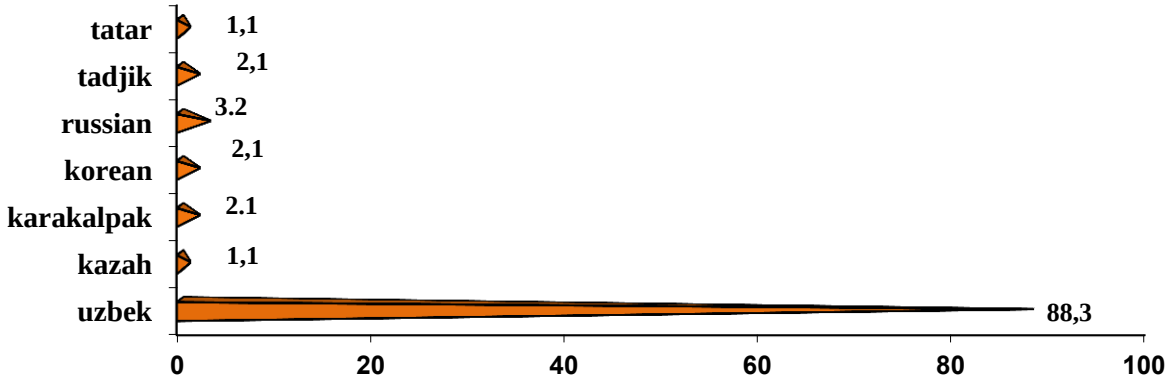
"Picture 1" Distribution of examined children by sex.

44.2% of patients in the main group at the time of diagnosis were aged 4-7 years, the smallest group consisted of children under the age of 3 years - 23.2%. In the comparison group, the age gradation of the applied patients ranged from 2 years to 14 years. 48.3% of patients at the time of diagnosis were aged 4-7 years, the smallest group consisted of children aged 8-14 years - 20.7% (Fig. 2.).



"Picture 2" Distribution of examined children by age

The average age in the main group was 7.8±0.48 years. The average age at the onset of the disease was 3.5±1.1 years. And in the comparison group, the average age 5.9±0.41. Children are sick from birth. Among the examined patients with NSP, the main group consisted of Uzbeks - 88.3%, the smallest group were Karakalpaks - 2.1%, Kazakhs - 1.1%, Tajiks - 2.1%, Russians - 3.2% (Fig. .3.).



"Picture 3" Distribution of children of the main group depending on nationality.

The largest number of patients of the main group applied from Tashkent city (17.9%) and Tashkent region (10.5%), which is associated with geographical proximity to the Republican Center for Screening of Mother and Child. In the regions of the republic, a high percentage of appeals was observed from Samarkand (15.8%), Kashkadarya (12.6%), and Surkhandarya regions (14.7%), which is most likely due to the high frequency of births, consanguineous marriages in these regions, and accordingly, the birth of a larger number of patients with this pathology (Table 1).

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Table 1

The number of patients with NSP by regions of the Republic of Uzbekistan (according to the appeal of patients to the Republican Center "Screening of mother and child") (n = 92)

Region	Quantity surveyed patients	
	Abs .	%
Tashkent city	17	17.9
Tashkent region	ten	10.5
Andijan region	3	3.2
Bukhara region	four	4.2
Jizzakh region	one	1.1
Republic of Karakalpakstan	2	2, 1
Kashkadarya region	1 2	1 2.6
Navoi region	one	1.1
Namangan region	5	5.3 _
Samarkand region	fifteen	15.8
Syrdarya region	four	4.2
Surkhandarya region	1 4	1 4.7
Ferghana region	2	2.1 _
Khorezm region	2	2.1 _
Total	92	96.9

However, there is an appeal for this disease from Russia 1 (1.1%), Tajikistan 1 (1.1%) and Kazakhstan 1 (1.1%).

According to the literature data [2,4,6], three types of NSP inheritance are described: autosomal dominant, autosomal recessive, and X-linked. It is believed that autosomal dominant spastic paraplegias are more common than autosomal recessive ones (55% versus 45% of the total number of patients with spastic paraplegia). According to our data, at in the study of the pedigrees of patients with NSP, in 34 cases the marriage was related, which amounted to 35.7%. It was found that in 48% of cases (27 families) there were patients with a similar disease in families. Depending on the distribution of consanguineous marriages by region, we were able to establish that the largest percentage was found in Kashkadarya, Samarkand and Surkhandarya regions (Table 2).

table 2

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Prevalence frequency of consanguineous marriages among surveyed children with NSP by regions of Uzbekistan

Region	Quantity surveyed patients	
	Abs .	%
Tashkent city	one	2.9
Tashkent region	2	5.9
Andijan region	one	2.9
Bukhara region	2	5.9 _
Jizzakh region _	one	2.9 _
Kashkadarya region	**6**	**17.7**
Navoi region	one	2.9
Namangan region	2	5.9
Samarkand region	**7**	**20.6**
Syrdarya region	2	5.9
Surkhandarya region	**6**	**17, 7**
Ferghana region	one	2.9
Khorezm region	2	5.9

The study and evaluation of large motor functions is necessary to assess the current clinical status of the patient and further prognosis, as well as monitoring the effectiveness of physiotherapy and medication, rehabilitation correction in patients with NSP and cerebral palsy. The assessment of large motor functions was carried out using the international scale for assessing large motor functions GMFCS (Fig. 4)

"Figure 4" GMFCS International Gross Motor Function Scale (Gross Motor function classification System)

The severity of spasticity was determined using the Ashworth scale. Ashworth Scale - Scale) is used to measure spasticity and the effect of treatment, as well as to measure the severity and frequency of resistance to passive movements on a five-point score (Table 3) .

Table 3

Modified Spasticity Scale Ashfort

Degree, score	Changes
0	No increase in tone
one	Slight increase in muscle tone, minimal tension at the end of the range of motion during flexion or extension of the affected limb
1+	Slight increase in muscle tone that occurs when grasping objects and is accompanied by minimal resistance (less than half of the range of motion)
2	More pronounced increase in muscle tone in most of the range of motion, but passive movements are not difficult
3	Significant increase in muscle tone - significant difficulty in passive movements
four	Rigid flexion or extension of the limb

The study of the motor sphere consisted in determining muscle strength, while motor activity was assessed by MRC (Medical Research Council) scale. This scale for assessing motor activity is presented as a 5-point scale, starting from 0 - the absence of any movements to 5 points - the presence of active movements in full, and is carried out as follows:

M 0 - there are no contractions in the muscle;

M1 - flickering abbreviations ;
M 2 - muscle contraction with active movement in the direction of gravity;
M 3 - full range of motion against gravity;
M 4 - full range of motion against gravity with little resistance;
M 5 - full range of movement against gravity with maximum resistance for the muscle under study.

When analyzing the obstetric anamnesis of the main group, it was found that the pregnancy proceeded in 32.6% against the background of anemia, in 10.5% - toxicosis. 10.5% of mothers suffered SARS during pregnancy. Exacerbation of chronic diseases during pregnancy was recorded in 8.4% of mothers of sick children. In 67.4%, the pregnancy was uneventful. It was found that in mothers of children with cerebral palsy, the 1st and 2nd half of pregnancy proceeded with complications, accompanied by toxicosis, threatened miscarriage, anemia, etc. Anemia of the II degree during the 2nd half of pregnancy was in 48 (82.4 %), ARVI - in 21 (36.2%), toxicosis - in 26 (44.8%), the threat of abortion - in 14 (24.1%) women (Table 4).

Table 4

Risk factors during pregnancy

current _ pregnancy	Main Group n=95 (100%)	Group comparisons n=58 (100%)	R
Anemia	31 (32.6%)	48 (82.8%)	0.001
Toxicosis	10 (10.5%)	26 (44.8%)	0.001
SARS	10 (10.5%)	21 (36.2%)	0.001
Nephropathy	7 (7.4%)	7 (12.1%)	
The threat miscarriage	2 (2.1%)	14 (24.1%)	0.001
Aggravation chronic diseases	8 (8.4%)	6 (10.3%)	
Pregnancy flowed without features	64 (67.4%)	8 (13.8%)	0.001

When studying the risk factors of the perinatal period, we found that in the main group, childbirth in 85.2% of cases proceeded without features, in 7.4% of cases premature. 9.5% of children were born with asphyxia. The birth weight of children averaged 3453.6±71.6 g (Table 5).

Table 5

Factors risk perinatal period

Factors	Main Group	Comparison group _	R
Childbirth without features	81 (85.2%)	22 (37.9%)	0.001
Premature childbirth	7 (7.4%)	36(62.1%)	0.001
Timing childbirth (weeks)	38.53±2.7	32.72±4.4	0.000
Gluteal and pelvic presentation	3(3.2%)	6 (10.3%)	
Detachment placenta	-	3 (5.2%)	
Early outpouring amniotic waters	-	24 (41.4%)	0.001
childbirth co stimulation	-	3 (5.2%)	
childbirth independent	88 (92.7%)	46 (79.3%)	0.05
Caesarean section	7 (7.4%)	9 (15.5%)	
polluted water	4 (4.2%)	21(36.2%)	0.001
EU at birth , gr	3453.6±71.6	2442.6±107.45	0.000
shouted straightaway	84 (88.4%)	21 (36.2%)	0.001
shouted weakly	2(2.1%)	10 (17.2%)	0.002
Asphyxia	9 (9.5%)	27 (46.6%)	0.001
Artificial lung ventilation	-	9 (15.5%)	0.002
About the Intensive Care Unit	-	23 (39.7%)	0.001
About the neonatal pathology department	3 (3.2%)	16 (27.6%)	0.001
Coma	-	2 (3.4%)	
Attached to the breast in the delivery room	91 (95.8%)	17(29.3%)	0.001
Feeding through probe	2 (2.1%)	29 (50%)	0.001
jaundice	7 (7.4%)	8 (13.8%)	

According to anamnestic data, in the comparison group, early rupture of amniotic fluid was in 24 (41.4%), contaminated water - in 21 (36.2%); 27 (46.6%) children were born with asphyxia. The birth weight of children averaged 2442.6 ± 107.45 g. An analysis of the term of delivery revealed that in the main group, term births occurred in 85.2% of cases, in the comparison group, preterm births prevailed 58.6% (Table 6).

Table 6

Terms of delivery	Main group	Comparison group
Less than 28 weeks	-	2 (3.4%)

28-35 weeks	7 (7.4%)	34 (58.6%)
36-40 weeks	81 (85.2%)	22 (37.9%)
Over 40 weeks	7 (7.4%)	-

An analysis of the development of psychomotor skills in the examined children showed that in the main group, in 70.4% of children, psychomotor development corresponded to age. 29.6% of patients started walking late, these children had a tendency to walk on tiptoe. The psychomotor development of children in the comparison group in 85.1% of cases did not correspond to the age norm, they lagged behind in psychomotor and speech development from birth.

We compared the clinical and neurological picture of NSP and cerebral palsy of spastic diplegia. The results of the neurological examination, shown in Table 7, indicate that in patients of the comparison group, clinical symptoms, especially changes in the craniocerebral innervation and motor sphere, were more pronounced than in the main group. A distinctive feature in the clinical picture was the presence of foot contracture in 65.2% of children with NSP (Friedreich 's foot), while in children with cerebral palsy, contracture of the ankle joint was more common, which amounted to 36.2% (P<0.001). Pelvic dysfunctions occurred in both groups, but more often in children in the comparison group. In the examined children of both groups, some clinical similarities were revealed: in both groups, gait disturbances were observed, i.e. typical spasmodic gait, movement disorders often asymmetrical, hyperreflexia, positive foot pathological signs.

Table 7

The frequency of occurrence of individual symptoms in the examined children

No.	signs diseases	Frequency symptoms				R
		Main group (n=95)		Group comparisons (n = 58)		
		Abs .	%	Abs .	%	
one	Circle heads					
	Normal	92	96.8	42	72.4	0.001
	Hydrocephalus	one	1.05	5	8.6	0.05
	Microcephaly	2	2.10	eleven	18.9	0.002
2	CHMN					
	violation vision	one	1.05	5	8.6	0.05
	converging strabismus	5	5.3	31	53.4	0.001
	divergent strabismus	3	3.2	fourteen	24.1	0.001
	Ptosis	2	2.1	-	-	

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	violations _ chewing	2	2.1	23	39.6	0.001
	violations hearing	-	-	3	5.1	
	violation swallowing	-	-	eleven	19	0.001
	speech (dysarthria)	6	6.3	47	81	0.001
3	Motor sphere					
	muscular tone					
	promoted on spastic type	95	100	58	100	
	Contracture					
	in the elbow joints	-	-	7	12.1	0.05
	in the wrist joints	-	-	5	8.6	0.05
	in the knee joints	eight	8.4	17	29.3	0.002
	in ankle joints	12	12.6	21	36.2	0.001
	foot " Fredreich "	62	65.2	-	-	0.001
four	sensitive violations	ten	10.5	5	8.6	
5	tendon reflexes					
	Promoted	95	100	58	100	
	with increased reflexogenic zone	95	100	31	53.4	
6	Positive foot signs					
	Babinskiy	95	100	58	100	
	Gordon	95	100	37	63.8	0.001
	Sheffer	95	100	21	36.2	0.001
	Oppenheim	95	100	29	fifty	0.001
	Clonuses	68	71.6	fourteen	24.1	0.001
7	Pathology coordinating spheres					
	intentional tremor	-	-	-	-	
	cerebellar ataxia	-	-	-	-	

During the clinical and neurological examination of patients with NSP, we revealed both pure spastic paraplegia, characterized only by motor disorders (82.1%), and spastic paraplegia with complications (17.8%) in the form of CCI dysfunction, intellectual impairment of varying degrees (9.4%), dysfunctions of the pelvic organs (7.3%), a history of seizures (5.2%), polyneuropathies (11.5%), extraneural symptoms were detected in 3 (3.1%) patients, i.e. congenital skin changes in the form of ichthyosis.

When assessing large motor functions on the GMFCS scale, the following indicators were revealed (Table 8): in both groups at the age of 4-7 years, levels 2 and 4 prevailed (72.7% and 77.6%). In the main group at the age of 8-15 years, level 5 prevailed - 21 (22%), while in the comparison group this figure was 4 (6.9%).

Table 8

GMFCS by age in surveyed groups.

Group		GMFCS level	Distribution on age			Total
			up to 3 years	4-7 years old	8-15 years old	
Main group	GMFCS χ2-77.49 P=0.000 R=0.66 P=0.000	2.0	twenty	fourteen	four	38
		3.0	one	one	one	3
		4.0	0	26	5	31
		5.0	one	one	21	23
	Total		22	42	31	95
Comparison group	GMFCS χ 2-6.6 P \u003d 0.36 R =-0.18 P =0.172	2.0	four	eight	7	19
		3.0	3	6	0	9
		4.0	ten	12	four	26
		5.0	one	2	one	four
	Total		eighteen	28	12	58

When evaluating spasticity using the Ashworth scale, in the main group 2 points did not occur, while in the comparison group this figure was 8.7% (Table 9). In the main group at the age of 4-7 years, 4 points prevailed (92.6%), while in the comparison group 3 points prevailed (50%).

Table 9

Assessment of spasticity in the lower extremities on the Ashworth scale in both groups.

Main group	Points	Age distribution			Total
		Up to 3 years	4-7 years old	8-15 years old	
Ashworth					

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n/a χ2-16.89 P =0.000 R = 0.3 _ P= 0.002	3 four	6 16	0 42	one thirty	7 88
Total		22	42	31	95
Comparison group	Points	Age distribution			Total
		Up to 3 years	4-7 years old	8-15 years old	
Ashworth n/a χ2-3.1 P =0.79 R = 0.11 _ P= 0.4	 2 3 four 5	 2 9 7 0	 3 13 eleven one	 0 7 four one	 5 29 22 2
Total		eighteen	28	12	58

Muscle strength on the M RC scale in the main group averaged 3-4 points (64.2% and 25.2%), while in the comparison group this figure was 2-3 (51.7% and 36.2%) points (Table 10).

Table 10

Assessment of muscle strength on the MR C scale in the examined groups.

Main group	Points	Age distribution			Total
		Up to 3 years	4-7 years old	8-15 years old	
MRC n/a χ2-55.5 P =0.000 R = - 0.535 P= 0.000	 2 3 four	 0 16 6	 one 41 0	 3 ten eighteen	 four 67 24
Total		22	42	31	95
Comparison group	Points	Age distribution			Total
		Up to 3 years	4-7 years old	8-15 years old	

MRC n/a χ2-7.4 P =0.493 R = 0.05 P = 0.7	 one 2 3 four 5	 0 ten 7 0 one	 one 12 eleven four 0	 0 eight 3 one 0	 one thirty 21 5 one
Total		eighteen	28	12	58

Primary health care physicians, when examining children with impaired motor functions and rapid progression of the pathological process, must necessarily refer this group of children for consultation of narrow specialists (medical genetics, neurologists, orthopedists, cardiologists, etc.) to exclude NSP.

Conclusions: In patients with NSP, movement disorders appear later by the age of 3 years and slowly progress thereafter. Already at the age of 10-12 years, patients are forced to use auxiliary means of transportation. And with cerebral palsy of spastic diplegia, compared with NSP, from birth, the clinical picture is characterized by a lag in psychomotor development and a non-progressive course. In case of clinical verification of NSP disease, it is necessary to conduct confirmatory molecular genetic diagnostics. The first step is to conduct MLPA diagnostics to detect large deletions and duplications in the SPG 4 gene. In the absence of deletions of the examined exons, sequencing of the SPG gene is recommended.

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