The cerebellum in children with spastic cerebral palsy: Volumetrics MRI study

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ABSTRACT

Purpose: To determine the volume of the cerebellum in children with spastic cerebral palsy (CP) in relation to risk factors and motor development.
Material and methods: The present study included 30 children with spastic CP, aged 2-17 years. The volume of the cerebellum was examined on sagittal magnetic resonance images (MRI) of the CP patients and on 33 healthy subjects. To estimate the total cerebellum volume of each subject we used Analyze 10 Biomedical Imaging Software.
Results: Children with spastic CP (129726,2 ± 26040,72 mm^3) had a significantly smaller mean of the cerebellum volume compared to controls (143122,5 ± 12351,10 mm^3). No significant difference between the total cerebellar volume and gender in patients with CP was found. No significant relationship between cerebellar volume and birth weight, Apgar score, gestational age, and Gross Motor Function Classification System (GMFCS) level were noted. Positive correlations between birth weight, Apgar score, gestational age, and GMFCS level, between Apgar score and gestational age, or between gestational age and GMFCS level were found.
Conclusion: Our results show that children with spastic CP had smaller volumes of the cerebellum as compared to controls.
Key words: MRI, semi-automatic cerebellar volume estimation, spastic cerebral palsy

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INTRODUCTION

According to different statistics, cerebral palsy (CP) occurs with frequency from 1.5 to 3.0 per 1000 live births. Clinically, the disease is dominated by signs of injury: motor cortex (limb paresis), basal ganglia (involuntary movements), cerebellum (congruity disorder of movement and balance). Approximately, 30-40% of children with CP finds varying degrees of mental retardation in about 35% of cases of epilepsy. Impaired vision (strabismus, eye disease) is seen in 50% of children and approximately 25% of hearing dysfunction [1-3]. In recent years, there has been an increase in the number of new cases of CP by improving the care of a mother and a child. CP, due to the incidence and multiplicity of symptoms, is important medical and social problem [4-6]. Contemporary diagnostics of children with CP, apart from the neurological examination, psychological and speech therapy as well as the neurophysiologic evaluation EEG also uses neuroimaging such as magnetic resonance imaging (MRI) [7-9]. Reports of recent years indicate the potential to differentiate changes in the various forms of CP by the technique of MRI [9-12]. Changes in white matter can be demonstrated in children with spastic diplegia, and tetraplegia in the sequences of T1 and T2 and FLAIR [10-12]. The cerebellum plays the most important role in motor coordination gathers information from many centers of the brain, analyzing them quickly and appropriately modulates that movements were smooth and accurate [13-14]. The cerebellum constantly monitors the course of the movement and coordinates the auto-patch as well as changes the voltage of other skeletal muscles to restore balance. The cerebellum also regulates: tone (tension) muscle, balance, learning motor behavior (i.e. cycling), smoothness and precision of voluntary movements (by motor interacts with the surroundings of the cerebral cortex), to name of few. Despite the great importance of the cerebellum, there is still insufficient knowledge to justify the reports of its dysfunction in patients with CP. The cerebellum is the subject of various studies and research in this field [6,7,13,14]. Based on the existing literature. We hypothesized that CP children would demonstrate smaller cerebellum volume and that these changes would be associated with more severe motor delay and mental development. In the present study, we present the results of volumetric studies of children with CP with the relation to age gender, Apgar score, gestational age, and motor development of patients.

MATERIAL AND METHODS

Subjects

Our quantitative MRI measurements were made on existing MRI data sets from previous, prospective MRI scans that were performed for clinical diagnostic purposes at Children's University Clinical Hospital of Białystok. The study was approved by the ethics committee of the Medical University of Bialystok. The subjects consisted of two groups - a patient group and controls. The patient group consisted of 30 subjects with CP (aged 2-17 years, 21 males and nine females). All CP individuals included into the study were had CP (diplegia spastica, tetraplegia, hemiplegia dextra or sinistra). In each case of CP, the diagnosis was confirmed by authors. Children with postnatal meningitis, encephalitis, trauma, and metabolic or degenerative disorders were excluded from the study. The control group included 33 healthy children (aged 4-19 years with mean value of age 11.12 and 4.77 SD; 16 males, 17 females). The subjects in the control group were healthy individuals without any known history of any disease as well as were free of any psychiatric or neurological abnormalities. MRI were normal. All the control subjects were right-handed.

Motor Function

Each child was classified according to the Gross Motor Function Classification System (GMFCS): level 1, walks without restrictions; level 2, walks without assistive devices, limitations in walking outdoor; level 3, walks with assistive devices; level 4, self-mobility with limitations, children are transported or use powered mobility; and level 5, self-mobility is severely limited.

Definitions

Cerebral palsy was classified as spastic tetraplegia (spasticity of all four limbs and of about equal involvement), and spastic diplegia – spasticity of lower limbs more affected than the upper. Hemiplegic CP refers to one arm and leg on either the right or left side of the body being affected [1]. Prematurity was defined by the World Health Organization as an infant with a gestation of less than 37 weeks from the first day of the last menstrual period. Asphyxia is defined as an Apgar score ≤ 4. Diagnosis of mental abnormality was based on clinical assessment, supplemented by standard tests if available at the time of diagnosis, and the need for special education. Epilepsy was defined as a separate occurrence of two or more apparently unprovoked seizures [15].

Magnetic Resonance Imaging and Acquisition

The MRI's brain datasets have been obtained at Department of Imaging Diagnostic in Children's University Clinical Hospital of Bialystok on the same 0.35 T Siemens Magnetom C scanner using the standard 4-channel head coil. A set of sagittal T1-weighted images were acquired with the following scan parameters: a time repetition (TR) of 20 ms, a time echo (TE) of 8.9 ms and a flip angle of 45°. Each volume consists of

between 124 and 128 sagittal slices, and each slice has dimensions 256 x 256 pixels. Voxel's dimensions were 0.9 x 0.9 x 5 mm. Routinely, brain data sets were saved and stored in a standard DICOM format controlled by Kodak DirectView OSM (Eastman Kodak Company, USA) storing system. For post acquisition processing of MR images, the DICOM files were transferred into a Window controlled desktop PC where they were processed using specialized image data processing software.

Image Analysis

To estimate the total cerebellum volume of each subject there were two important stages to perform, MRI data pre-processing and the cerebellum segmentation (Figure 1). For both of them dedicated tools implemented in the Analyze 10 Biomedical Imaging Software (AnalyzeDirect, Overland Park, KS, USA) were used. In the first stage, two databases have been created by using DICOM Tool of the Analyze 10. Collected the original MRI DICOM volumetric data were then converted to internal volumetric AVW format. To prepare for further brain segmentation each set has been also linearly interpolated to isotropic matrix. In the second stage, the cerebellar volume of the individual was manually estimated in a slice-by-slice fashion according to the following procedure. After loading a set of T1-weighted sagittal images into the Analyze 10 workspace the midline slice was chosen, and segmentation was initialized by introducing a seed point approximately in the center of the 2D cerebellum region. Next, manipulating manually with thresholding value the cerebellum boundary tracing was performed using ROI Defining and Measurement Tool of Analyze 10. When the contour of the cerebellum has been successfully drawn then it was replicated over all sagittal slices where the cerebellum were visible. However, for each slice the anatomical correctness of the cerebellum segmentation was examined visually by the rater and often corrected due to permanent changes in geometry of boundary between region of the cerebellum and adjacent structures of the whole brain. To isolate the individual cerebellum, the cerebellar mask was created in cooperation with an expert radiologist. Having defined the mask, it was possible to calculate cerebellum volume by multiply defined ROI's by slice thickness. Finally, using the manual procedure of segmentation, we separated cerebellum from the brainstem and cerebellar penducles. The resulting volumes consisted of the volumes of the vermis, cerebellum hemispheres and deep nuclei. Because both age and gender are known to affect cerebellum volume brain size, data were analyzed with covariance for age and sex to account for any potential influences on comparisons.

Statistics

To assess the effects of age and gender on the cerebellum volume (CV), the absolute CVs were firstly analyzed to examine the linear relationship between CV and age using regression analysis. Then one- and multifactor analysis of variance with gender and CONDITION – CP as factors and cerebellum volume as a dependent variable was carried out. Finally non-parametric analysis of variance (ANOVA) was performed to verify the results of multifactor analysis of variance (MANOVA) due to statistically significant result of variance homogeneity test. All analyses were considered as statistically significant when a p-value was less than 0.05. The data analyses were performed with statistical data analysis software STATISTICA Ver. 9.0 (StatSoft, Inc., Tulsa, OK, USA).

RESULTS

The study group was composed of 30 children with CP (21 boys, nine girls). There were more boys than girls in the CP group, but did not differ significantly ($p=0.077$). The ages of the children when first seen ranged from 2 to 17 years, with a mean age of 6.33 ± 4.06 years. The control group included 33 healthy children (aged 4-19 years with mean value of age 11.12 ± 4.77; 16 males, 17 females). There was the significant age difference between groups ($p<0.001$). The clinical data are summarized in Table 1. Thirteen children 13 had spastic diplegia, 8 children had spastic tetraplegia CP, and 9 had spastic hemiplegia. Nine (30%) patients had epilepsy. Preterm birth was noted in 10 (33%) patients. Asphyxia was recorded in 10 (33%) children with CP. Cesarean section was performed in 9 (30%) patients.

Descriptive statistics

The values of descriptive statistics are presented in Table 2. Total cerebellar volume was decreased significantly in MRI studies performed at patients with CP, compared with healthy children (129726,20 ± 26040,72 vs. 143122,50 ± 12351,10; $p<0.001$). The mean difference was approximately 9.4%. No significant difference between total cerebellar volume and gender in patients with CP was detected. In contrast, a significant ($p<0.001$) between total cerebellar volume and gender in the control group was found. Boys had a lager total cerebellar volume than girls. The mean difference was approximately 10.3%. Partial graphical representation of descriptive statistics is presented in Figures 2-4.

Correlation analysis

Correlation analysis was carried out in patients with CP and controls. Variables for which the strength of linear relationship was examined were age and cerebellum volume. No relationships

between gender and the cerebellum volume in CP patients and in controls were found (Table 3).

Analysis of variance

One-way analysis of variance was conducted on two data sets defined by levels of variable CONDITION. Variable gender was taken as a factor. Two-way analysis of variance was conducted on a data set containing all cases, with levels of factors defined by variables gender and CONDITION. The results of one-way and two-way analysis of variance are summarized in Table 4 including values of F statistic (including degrees of freedom) and p-values. Results were considered significant when ($p<0.05$) and are marked with bold font. One-way analysis of variance was carried out separately for healthy and CP children with grouping variable gender. Significant differences in mean values of volume among healthy children was found. Significant differences between gender and CONDITION were taken as factors were found in two-way analysis of variance. No significant differences were detected for interaction of factors. Although p-value level obtained for interaction of factors was not significant, post-hoc analysis was carried out because of the results of one-way ANOVA. Ducan test was used and at significance ($p<0.05$) it showed, that there is one group significantly different from the rest: CONDITION = Controls, gender = M. Remaining groups, defined by different combinations of factor levels (Controls-CP-F, CP-F, CP-M), form a second group – with no significant differences in their mean values of volume. Factor gender has a significant influence on mean values of volume, the same as factor CONDITION –in both cases p- vale was (< 0.05).

Results of linear regression analysis

No relationship between cerebellar volume, birth weight, Apgar score, gestational age, and GMFCS level were noted (Tab. 5). Positive correlations between birth weight, Apgar score, gestational age, and GMFCS level, between Apgar score and gestational age, or between gestational age and GMFCS level were found.

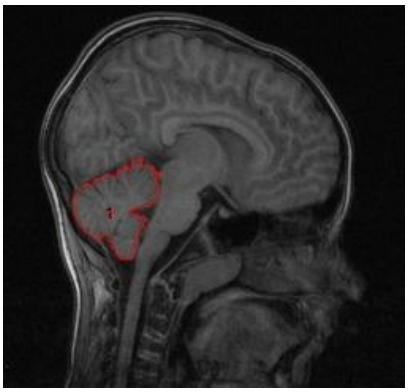

Figure 1. MRI of patient with cerebral palsy (CP). Example of the cerebellum segmentation using Analyze 10 Biomedical Imaging Software.

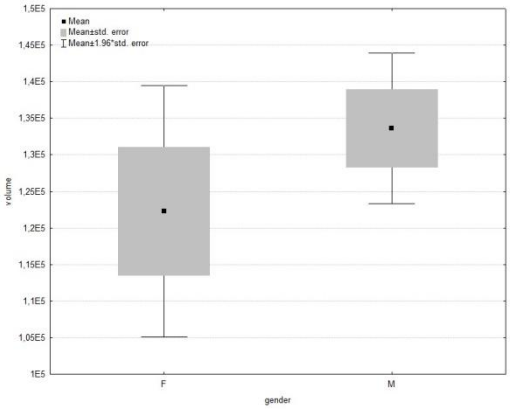

Figure 2. Cerebellum volume in children with spastic cerebral palsy (CP) with relation to gender.

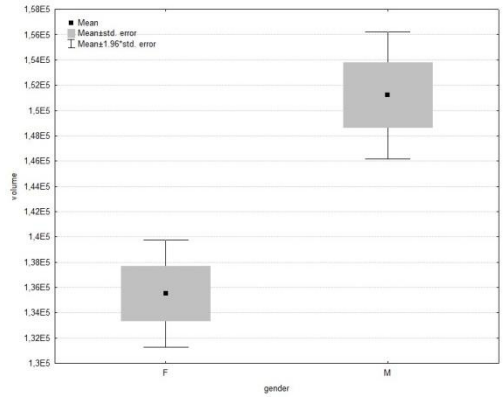

Figure 3. Cerebellum volume in the control group with relation to gender.

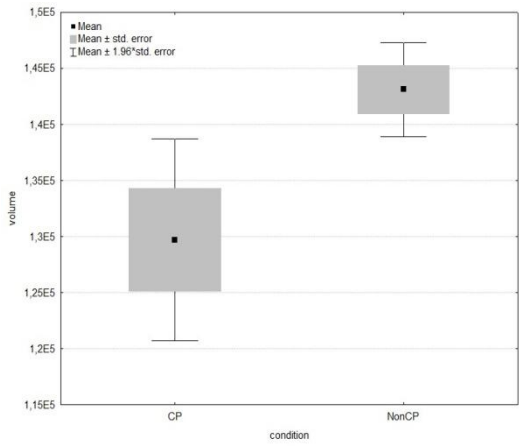

Figure 4. Comparison of cerebellum volume in children with spastic cerebral palsy (CP) and controls.

DISCUSSION

This study has demonstrated that CP group had a significantly smaller mean of the cerebellum volume than did the control group. Positive relationship between cerebellar volume and age in children with CP and controls was found. No significant difference between total cerebellar volume and gender in patients with CP was detected. In the control group, boys had a lager total cerebellar volume than girls. Our findings are in agreement with previous studies [11,16,17]. Bodensteiner and Johnsen [11] reviewed 94 brains MRIs of children with CP whose birth weight was less than 1000 g and whose gestational age was less than 28 weeks. The common cerebral abnormalities included decreased white-matter volume without gliosis (n=36), periventricular leukomalacia (n=16), and a thin corpus callosum (n=18). Cerebellar abnormalities were found in 32. The cerebellar findings included destruction of major portions of the cerebellum (usually the inferior vermis and hemispheres) and focal or unilateral loss of cerebellar tissue. The pattern of cerebellar injury suggests a vascular insult, and the deficient white matter without gliosis suggests immaturity of oligodendrogliocytes with the limited response to injury. In our study, common MRI finding was also periventricular leukomalacia - 19 cases. And all patients had normal cerebellar imaging. Similar findings described Srinivasan et al. [15] determining the absolute cerebellar volumes in term and preterm infants in correlation with risk factors. The median cerebellar volume of preterm was significantly smaller as comparing to term-born infants. Moreover, in the multiple regression analysis of perinatal variables showed that only infants with supratentorial lesions were significantly associated with the reduction in cerebellar volumes. In other study, [17] children with spastic CP had a significantly smaller mean of the cerebellar hemispheres and the brain stem than did controls. The cerebellar volumes were positively correlated with age of children with CP and the control group. No significant correlations between gender and the volumes of cerebellar hemispheres and the brain stem in controls and in the CP group were found. No significant correlations between asphyxia and the volumes of cerebellar hemispheres and the brain stem in the CP group were noted. Positive correlation between the cerebellum volume and mental development in children with CP was found. Negative relationship between the cerebellar hemispheres volume and GMFCS in patients with CP was found. Results from animal studies suggest a causal relationship exists between motor skill acquisition and practice and structural changes in the cerebellum [18,19]. The traditional view of cerebellar function has expanded from one of the motor coordination to involve motor skill acquisition [18,19] and varied cognitive and sensory discrimination tasks [20]. Furthermore, in the present study, we did not include CP children with ataxia. We evaluated only children with spastic CP. Many children with CP have poor walking abilities and manipulation skills. Balance and motor coordination in CP patients is often impaired [21]. One contributing factor to their problems with gait and reaching movement is poor balance control because the maintenance of stability is critical to all movements. There is a general agreement that the cerebellum is involved in motor coordination and learning, although the exact role of the cerebellum is still a matter of discussion [22]. More recently, an additional role of the cerebellum in pure cognitive function has been proposed [20,23]. In the last decade, an increasing number of studies in cerebellar patients and in healthy subjects using functional brain imaging techniques claimed evidence for an involvement of the cerebellum in mental skills [23,24]. In the current study, we did not examine the mental development of children with CP. To estimate the total cerebellum volume of each subject, there were two important stages to perform, MRI data pre-processing and the cerebellum segmentation. For both of them, dedicated tools implemented in the Analyze 10 Biomedical Imaging Software were used. In principle, there are a number of sources of potential error in the data acquisition and analysis system employed here [25,26]. These include image artifacts (intensity drift, motion and pulsatile phase artifacts, susceptibility effects), errors in segmentation, and the use of multiple scanners with variation in imaging sequence parameters. Our use of a semi-automated segmentation system gives the segmenter the flexibility to adjust for the majority of minor image anomalies such as intensity artifacts due to susceptibility changes and phase artifacts. Images which possess an unacceptable level of an artifact are not analyzed and the imaging is reprogrammed These and previous studies [16,27,28] have demonstrated no significant differences in volumes determined using the scanners and parameters similar to ones used in this study. Caviness et al. [16] performed volumetric MRI-based morphometry on the brains of 30 normal children with a mean age of nine years (range 7-11 years). They found that females, unlike males, reach adult cerebellar volume earlier in childhood, at this time both genders have equivalent relative cerebellar volumes. The brain at this age is 95% the volume of the adult brain. The brain of the female child is 93% the volume of the male child. The development of the human brain is a dynamic process that continues throughout gestation. Cortioconeurogenesis refers to the process of neural development and the connectivity between the various layers of the brain. Subcortical neurons are detectable as early as 10-week gestation. However,

neuronal proliferation continues through mid-gestation, and the maturation process continues to the end of gestation [29]. There is a linear increase in brain volume with increasing gestational age in cerebral and cerebellar tissues. During the last five weeks of gestation, there is a significant increase in dendritic connections and sulci formation. In the present study, one-third of patients was born preterm, on the other hand most 60% was born in term. The preoligodendroglia are the precursors to the developing white matter. They are uniquely vulnerable to injury in infants born prematurely. The magnitude of potential injury is significant when one considers that this is the dominant cell lineage in the developing white matter between 28 weeks and 41 weeks gestation [29,30]. Furthermore, the critical phases of axonal synaptogenesis, maturation and elongation, still need to occur during the latter half of gestation. These data are in part responsible for the increased risk for white matter injury in the preterm infant [11,31]. Over the last decade, increasing evidence of cognitive functions of the cerebellum during development and learning processes could be ascertained [32,33]. Posterior fossa malformations such as cerebellar hypoplasia are known to be related to developmental problems in a marked to moderate extent. More detailed analyses reveal special deficits in attention, processing speed, visuospatial functions, and language. Acquired cerebellar or vermis atrophy was found in groups of children with developmental problems such as prenatal alcohol exposure, extreme prematurity or CP. In addition, cerebellar atrophy was shown to be a bad prognostic factor considering the cognitive outcome in children after brain trauma. Our results are in agreement with previous clinical and neuroradiologic reports on CP [7,8,9,11,12]. The MRI findings may help us to understand not only the type of lesion but also the timing of insult. It is particularly important to perform MRI in all children with motor impairment (e.g., difficulty in sitting or standing) to detect brain abnormalities such as periventricular leukomalacia, cerebral atrophy, or porencepahly. The association between cerebellum volume in the early childhood and neurodevelopmental outcome highlights its importance as a useful clinical indicator in the follow-up of high-risk preterm and term infants. Early detection of brain abnormalities in children with CP may help in prognosis and in the initiation of appropriate therapy (rehabilitation of motor impairment or language therapy). This study has some limitations such as lack of the mental developpment, visual and language studies of patients with CP.

CONCLUSION

The present study demonstrated that children with spastic CP had smaller volumes of the cerebellum as compared to controls.

Table 1. Clinical data of children with spastic cerebral palsy (CP).

Patient	Age (years)	Sex	Birth weight (kg)	Apgar	Gestational age /Pre-perinatal history (weeks)	CP type	Epilepsy	MRI	GMFCS
1	8	M	1050	1	27	Tetra	Yes	PVL	4
2	13	F	3700	6	39, CS	HemD	Yes	MCAI	1
3	8	F	2700	1	35, S	Tetra	Yes	PVL	3
4	5	M	3900	10	40, CS FDS	HemD	No	PVL	1
5	3	F	2480	6	37, TP	Dip	No	N	1
6	5	M	2800	8	34	Dip	No	PVL, CCT	1
7	10	F	2680	9	38, S	Tetra	Yes	CA	4
8	7	M	2950	9	38, CS FD	Tetra	Yes	CA	4
9	18	F	2500	1	38	Tetra	No	PVL	2
10	7	M	3800	9	37	Dip	No	PVL	1
11	9	M	3050	4	40, CS	Dip	No	PVL	2
12	7	M	900	2	25 CS, B	Tetra	No	PVL	4
13	3	M	2800	3	32	HemS	No	PVL	1
14	1	M	3040	10	37	Dip	No	N	1

Patient	Age (years)	Sex	Birth weight (kg)	Apgar	Gestational age /Pre-perinatal history (weeks)	CP type	Epilepsy	MRI	GMFCS
15	11	M	2600	4	34	Dip	Yes	PVL	2
16	4	M	3650	10	39	Dip	No	PVL	1
17	13	M	2100	7	37	Tetra	No	CA	4
18	3	M	2800	6	34	Dip	No	PVL	2
19	2	M	3500	10	38	HemD	No	PVL	1
20	8	F	3300	5	38	HemD	No	PVL	1
21	4	M	4350	10	42	HemD	No	PVL LS	1
22	1	M	3350	9	40	HemD	No	PVL LS	1
23	2	F	1100	4	28	Dip	No	PVL	3
24	11	F	3600	3	38, CS	HemS	No	PLL	1
25	2	M	3000	8	38	Dip	No	PVL	2
26	3	M	2800	7	37, CS	Dip	No	PVL	2
M-male, F- female, B - bleeding, S - sepsis, N - normal, CP- cerebral palsy, CS-cesaren sectio, CA-cerebral atrophy, Dip-diplegia, TP - twin pregnancy, LS - left side, CCT - corpus callosum thin, PLL -porencephaly left lobe, FDS-fetal distress, HemD-hemiplegia dextra, HemS-hemiplegia sinistra, Tetra- tetraplegia, Hem-hemiplegia, PVL- Periventricular leukomalacia, MCAI- Middle cerebral artery infarct.									

Table 2. Cerebellum volume in children with spastic cerebral palsy (CP) and controls related to gender.

	No subjects	**Mean**	**Median**	**Minimum**	**Maximum**	**Variance**	**Std. Dev.**
Volume of the cerebellum (mm^3)	CP						
	30	129726,2	132721,5	74029,00	184156,0	678119144	26040,72
	Controls						
	33	143122,5	139655,0	112950,0	171219,0	152549657	12351,10
	CP, Gender = F						
	11	122279,7	122522,0	74029,00	162288,0	842632482	29028,13
	CP, Gender = M						
	21	133626,8	135382,0	94133,00	184156,0	583295854	24151,52
	Controls, Gender = F						
	17	135515,6	136599,0	112950,0	149757,0	79479164	8915,109
	Controls, Gender = M						
	16	151204,8	152690,5	134426,0	171219,0	105403359	10266,61
CP- cerebral palsy, M-male, F-female							

Table 3. Correlations between the cerebellar volume and age with respect to gender in patients with spastic cerebral palsy (CP).

CP			**Controls**		
GENDER=F	GENDER=M	No grouping	GENDER=F	GENDER=M	No grouping
R=0.33 P=0.31 N=11	R=0.26 P=0.26 N=21	R=0.19 P=0.29 N=32	R=0.39 P=0.13 N=17	R=0.36 P=0.17 N=16	R=0.06 P=0.73 N=33

Table 4. Results of one-way and two-way analysis

One-way ANOVA		Two-way ANOVA		
Factor = CONDITION		Factors		
CP	Controls	GENDER	CONDITION	Interaction
F(1,30)=1.39 P>0.24	**F(1,31)=22.05** **P<0.01**	**F(1,61)=7.48** **P<0.01**	**F(1,61)=9.71** **P<0.01**	F(1,61)=0.19 P>0.66

Table 5. Relations between the cerebellar volume and birth weight, Apgar score, gestational age and GMFCS in patients with spastic cerebral palsy (CP).

	Birth weight	**Apgar score**	**Gestational age**	**GMFCS**	**Cerebellar Volume**
Birth weight	R=1.0000 p= ---	**R=.6052** **p=0.001**	**R=.8676** **p=0.000**	**R=-.7231** **p=0.000**	R=.3523 p=.078
Apgar score	---	R=1.0000 p= ---	**R=.5903** **p=0.002**	R=-.3421 p=.087	R=.1094 p=.595
Gestational age	---	---	R=1.0000 p= ---	**R=-.5048** **p=0.009**	R=.3706 p=.062
GMFCS	---	---	---	R=1.0000 p= ---	R=-.1930 p=.345
Cerebellar Volume	---	---	---	---	R=1.0000 p= ---
R- regression coefficient; GMFCS - Gross Motor Function Classification System					

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