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Clinical and neuroimaging profile of congenital brain malformations in children with spastic cerebral palsy

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ABSTRACT

Purpose: Analysis of the incidence of congenital brain malformations in children with spastic cerebral palsy (CP) in a hospital-based study.
Material and Methods: The present study included 74 boys and 56 girls with spastic tetraplegia, diplegia, and hemiplegia CP. Magnetic resonance imaging MRI findings were analyzed in children with CP.
Results: Significant abnormalities relevant to the CP were evident on MRI in 124 (95.3%) subjects. Periventicular leukomalacia (PVL) was detected more frequently in children with spastic diplegia than in patients with tetraplegia or hemiplegia. Cerebral atrophy was found more often in the tetraplegic group compared to the diplegic patients. Porencephalic cysts were detected more often in children with spastic hemiplegia. Congenital brain anomalies were evident in 15 (10.7%) children with spastic CP. Brain malformations included: schizencephaly (5), agenesis corpus callosum (4), polymicrogyria (2), holoprosencephaly (2) and lissencephaly (2). Intractable epilepsy and mental retardation were observed more often in children with brain anomalies. Twelve patients with congenital brain malformations were born at term and three born at preterm.
Conclusions: Neuroimaging results in children with CP may help determine the etiology and make better prognosis of CP.

Key words: brain malformations, cerebral palsy, magnetic resonance imaging

INTRODUCTION

The successes of neonatal intensive care during the past two decades in reducing neonatal mortality have not been matched by success in reducing the risk of cerebral palsy (CP) . The perinatal mortality has decreased by 25% over the last decade, mainly due to the improvements in ventilatory management [1]. Rates of prematurity, though, have increased during the same time period [2], leading to an increased number of high-risk newborns that suffer from considerable neurologic morbidity – often associated with CP [3]. Lesions responsible for periventricular leukomalacia (PVL) and posthemorrhagic porencephaly are considered to occur early in the third trimester [4]. Both vascular and intrinsic metabolic factors are thought to be responsible for the localization of PVL. In patients with spastic tetraplegia, congenital abnormalities are often found in magnetic resonance imaging MRI [4,5]. Understanding the time of onset of a brain lesion in a child with CP and the potential preventability of the neurological injury is important for parents and the children themselves, and for medical professionals. Magnetic resonance imaging (MRI), in particular, provides detailed information about the brain lesions. More previous studies have analyzed MRI findings in patients with CP in relation to motor impairment [6,7,8]. The Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society have released a new guideline on neuroimaging tests for CP and related disorders [9]. The committee concluded that the detection of a brain malformation in a child with CP warrants consideration of an underlying genetic or metabolic etiology. Neuroimaging results in children with CP may help determine the etiology and make better prognosis of CP [5,10-15].

The aim of the present study is to analyze the incidence of congenital brain malformations in children with spastic CP.

MATERIALS AND METHODS

Subjects

We retrospectively evaluated children with CP referred to our Pediatric Neurology and Rehabilitation Department in Bialystok from January 2000 to August 2007. The present study included 130 children (74 males and 56 females, mean age 8.20 ± 4.48 years, range 3–17) with spastic tetraplegia, diplegia, and hemiplegia CP *(Tab. 1)*. The mean age of patients at MRI tests was 6.27 ± 2.30 years, range 3–17. Of these children, 46 had spastic tetraplegia CP, 40 had spastic diplegia and 44 had spastic hemiplegia. In each case of CP the diagnosis was confirmed by the authors. Children with postnatal meningitis, encephalitis, trauma after neonatal period and metabolic or degenerative disorders were excluded from the study.

Motor function

The children were each assigned a Gross Motor Function Classification System (GMFCS) level by a physical therapist according to [16]. Level I: walks without restrictions; II: walks without assistive devices, limitations in walking outdoors; III: walks with assistive devices; IV: self-mobility with limitations, children are transported or use powered mobility; V: self-mobility is severely limited.

Cognitive function

The patients were assigned to one of three groups, depending upon their level of academic achievement, supplemented by results of formal psychological testing: 1) Normal: normal school performance to at least first grade level, with no evidence of specific learning difficulties. All the children in this group had one or more formal psychological assessments (the typical Wechsler Intelligence Scale for Children, Polish version) [17]. 2) Mentally handicapped: formal psychological testing results indicated function in the mentally deficient range. 3) Mental retardation was divided into the following ranges: mild: 70-84 intelligence quotient (IQ); moderate: 50-69 IQ; severe: <50 IQ. Normal children had IQ > 90. Eleven children with spastic tetraplegia were not testable since based on behavioral observation they were too mentally impaired or uncollaborative to obtain a standardized score.

MRI

All MR scans were obtained using a 1.5 T MR scanner (Picker Edge Eclipse, USA) with the use of a standard circular-polarized head coil. The images were assessed by the neuroradiologists and separately by the child neurologists, unaware of the prenatal and perinatal histories or of the clinical evaluations. Cerebral atrophy was diagnosed when diffuse sulcal widening of the cerebrum with symmetrical ventricular dilatation without periventricular signal abnormalities was observed [18]. PVL was diagnosed in patients who had ventriculomegaly with irregular outlines of the body and trigone of the lateral ventricle, a reduced quantity of periventricular white matter, deep prominent cerebral sulci, and periventricular signal abnormalities of low intensity on T1-weighted images and high intensity on T2-weighted images [19]. We also analyzed the incidence of the following brain injures: posthemorrhagic porencephaly, middle cerebral artery infarct, multicystic encephalomalacia, polymicrogyria and congenital brain malformations (schizencephaly, lissencephaly, agenesis corpus callosum, holoprosencephaly). Imaging sequences: T1-weighted FAST pre- and post-i.v. contrast media administration (0.1 mmol/kg Megnevist, Schering) were performed [20]. FSE T2-weighted and FLAIR series were used.

Definitions

CP was defined as motor disabilities caused by non-progressive damage to the developing brain [21]. CP was classified as spastic tetraplegia (spasticity of all four limbs and with about equal involvement) and spastic diplegia (spasticity with the 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. Epilepsy was defined as a separate occurrence of two or more apparently unprovoked seizures [22]. The seizure outcome was defined as good if the patient was seizure-free for more than two years. Intractable epilepsy was defined as two seizures per month despite appropriate drug therapy (required two antiepileptic drugs) [3,23]. Epileptic seizures were divided into the following three groups: 1) partial (including simple partial, complex partial, and partial with secondary generalization); 2) generalized (generalized seizures other than infantile spasms , including tonic, tonic clonic, myoclonic, and atypical absence seizures); and 3) Lennox-Gastaut syndrome. Prematurity has been 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 neonatorum is respiratory failure in the newborn, a condition caused by inadequate intake of oxygen before, during, or just after birth.

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 need for special education.

Statistical analysis

The differences between the groups were determined by the parametric t-test and nonparametric statistical tests: Fisher's Exact test or chi-square test where appropriate. All P values were two-tailed. Statistical significance was defined as $P < 0.05$. Statistics were calculated using Statistica 6.0. The study was approved by the ethics committee of the Medical University of Bialystok.

Table 1. **Characteristics of subjects with spastic cerebral palsy.**

Variable	Tetraplegia (n=46)	Diplegia (n=40)	Hemiplegia (n=44)	P – value
Gestational age Range Mean, SD	 26-41 36.03 ± 3.78	 25-41 34.61 ± 4.58	 25-42 38.43 ± 3.29	NS
Male/female	26/20	22/18	27/17	NS
Preterm	25	23	9	
Term	21	17	35	NS
Apgar score at 1 min. < 4 > 4	 21 25	 14 26	 12 26	 NS NS
Weight at birth Range Mean, SD	 1100-4000 2650 ±795	 850-4150 2490 ± 1036	 1550-4200 3128 ± 755 * #	* <0.001vs diplegia # <0.001 vs tetraplegia
GMFCS levels, n				
I	0*#	19	17	* <0.001vs diplegia # <0.001 vs hemiplegia
II	1 *#	16	16	* <0.001 vs diplegia # <0.001 vs hemiplegia
III	10	5	5	NS
IV	24 *#	0	0	* <0.001 vs diplegia # <0.001 vs hemiplegia
V	11~•	0	0	~ <0.01 vs diplegia • <0.01 vs hemiplegia
Mental development				
Normal	0 ♦♣	10	15	♦ <0.01 vs diplegia ♣ <0.01 vs hemiplegia
Small delay	4 ♦♣	24	17	♦ <0.001 vs diplegia ♣ <0.05 vs hemiplegia
Mild	17	6	11	NS
Severe	25 ♦♣	0	1	♦ <0.01 vs diplegia ♣ <0.01 vs hemiplegia
Epilepsy	22	7 ♦♣	22	♦<0.05 vs tetraplegia ♣<0.05 vs hemiplegia

GMFCS- Gross Motor Function Classification System , p- value from t-test and Fisher's Exact test between groups. NS – not significant

RESULTS

The study group comprised 130 children with CP (74 boys, 56 girls). The clinical data are summarized for all patients in Table 1. Forty-six children had spastic tetraplegia CP, 40 had spastic diplegia, and 44 spastic hemiplegia. No differences in preterm and term between spastic tetraplegia, spastic diplegia and spastic hemiplegia were noted. Asphyxia was recorded more frequently in the tetraplegic CP group than in the spastic diplegic or spastic hemiplegic CP groups. Significant differences in the birth weight between hemiplegic CP and diplegic CP ($p<0.001$) or tetraplegic CP children ($p<0.001$) were observed.

Risk factors for CP

Fifty-six (43.0%) children with spastic tetraplegia, diplegia and hemiplegia CP were born preterm, and 74 (56.9%) in term. The prenatal risk factors of asphyxia and low birth weight were observed in 46 (35.6%) and 50 (38.7%) patients, respectively *(Tab. 2)*. Perinatal risk factors (prelabor rupture, abruptio placenta, fetal distress, pre-eclampsia, and sepsis) ranged from 4.5% to 48.8% in the spastic tetraplegic, diplegic and hemiplegic CP children (data are not shown). Male sex was not associated with an increased risk of tetraplegic, diplegic or hemiplegic CP, nor was gestational history related to an increased risk of tetraplegic, diplegic or hemiplegic CP. The percentages of caesarean sections in the groups were comparable. Low birth weight (<2500 g) was observed more frequently (but not significantly) in tetraplegic and diplegic CP than in hemiplegic CP. The perinatal pathologies (prelabor rupture, abruptio placenta, fetal distress, pre-eclampsia, and sepsis) were present in similar proportions in the tetraplegic, diplegic and hemiplegic CP groups.

GMFCS

A significantly greater number of children with spastic diplegia and hemiplegia were assigned to GMFCS levels I and II compared to tetraplegic group *(Tab. 1)*. On the other hand, the patients with spastic tetraplegia were assigned

Table 2. **Risk factors of children with spastic tetraplegia, spastic diplegia and spastic hemiplegia cerebral palsy.**

Variable	Tetraplegia N(%) (n=46)	Diplegia N (%) (n=40)	Hemiplegia N(%) (n=44)	P -value
Male sex	26 (56.5)	22 (55)	27 (61.3)	NS
Asphyxia	21 (45.6)	14 (35)	12 (27.7)	NS
Gestational history				
Preterm	24 (53.5)	23(55.2)	9 (20.4)	NS
Term	22(48.8)	17 (42.5)	35 (79.5)	NS
Post-term	0 (0)	0 (0)	0 (0)	
Caesarean section	15 (32.6)	12(30.0)	11 (25.0)	NS
Low brith weight < 2500g	22 (47.8)	19 (47.5)	9 (20.4)	NS
Pre-labour rupture of membranes	12 (26)	16 (40)	8 (18.1)	NS
Fetal distress	8 (17.4)	8 (20)	7 (15.9)	NS
Abruptio placenta	5 (10.8)	3 (7.5)	2 (4.54)	NS
Pre-eclamsia	4(8.7)	3 (7.5)	2.(4.54)	NS
Sepsis	4(8.7)	3(7.5)	2 (4.54)	NS

Fisher's Exact test , NS- not significant

Table 3. **Magnetic resonance imaging abnormalities in children with spastic cerebral palsy.**

MRI findings	Tetraplegia (%) N=46	Diplegia (%) N=40	Hemiplegia (%) N=44	P –value
Normal	0	4 (10.0)	2 (4.5)	NS
PVL	20 (45)	30 (75)	17 (38.6)	NS
Cerebral atrophy	13 (28.8)**	1 (2.5)	3 (6.8)	**<0.01 vs diplegia
Posthemorrhagic porencephaly	4 (8.7)	2 (5.0)	10 (22.7)	NS
Middle cerebral arteryInfarct	0	0	6 (13.6)	NS
Multicysticencephalomalacia	2 (4.3)	0 (0)	2 (4.5)	NS
Polymicrogyria	0	0	2 (4,5)	
Holoprosencephaly	1 (2.1)	1(2.5)	0	NS
Schizencephaly	2 (4.3)	1 (2.5)	2 (4.5)	NS
Lissencephaly	2 (4.3)	0	0	NS
Agenesis of corpus callosum	2 (4.3)	1(2.5)	0	NS

PVL- periventricular leukomalacia, NS- not significant

more frequently to GMFCS levels IV and V than the patients with spastic diplegia and spastic hemiplegia. The locomotion function was affected in similar proportions in the tetraplegic, diplegic and hemiplegic CP children with or without epilepsy (data are not presented).

Mental development

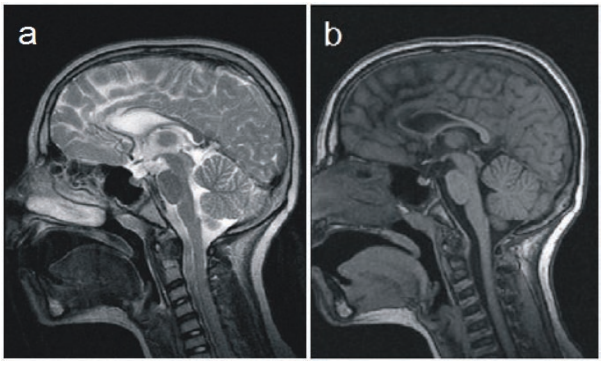
Similarly, the mental development differed significantly between the groups *(Tab. 1)*. Patients with normal and small delay in mental development were more frequently seen in the diplegic and hemiplegic CP groups compared to the tetraplegic CP group. On the other hand, severe mental retardation was observed more often ($p<0.01$) in the children with spastic tetraplegia CP than in the patients with spastic diplegia or spastic hemiplegia CP. Significantly ($p<0.05$) higher percentages of epilepsy were documented in the tetraplegic and hemiplegic CP groups – 21 (46.6%) and 22 (50.0%) respectively – compared to diplegic children. Among patients with spastic CP 13 children with congenital brain malformations had mental retardation. Only one child had normal development *(Tab. 3)*.

Epilepsy attacks in the CP group included partial seizures secondarily generalized in 11 children with spastic tetraplegia, generalized seizures in 3, infantile spasms in 4, Lennox-Gastaut syndrome (data are not shown). In the spastic hemiplegia and diplegia children, partial seizures secondarily generalized were the dominant type of convulsions.

MRI abnormalities

Cranial MRI studies were performed in all patients *(Tab. 2)*. Significant abnormalities relevant to the paresis were evident on imaging in 124 (95.3%). Six children had normal MRI scans. A similar percentage of MRI abnormalities were detected in the groups, 46 (100%) in patients with tetraplegic CP, 37 (92.5%) in children with diplegic CP, and 42 (95.4%) in those with hemiplegic CP. The most common finding on MRI

Figure 1. **10 year –old girl with tetraplegia and epilepsy. Sagital MRI a) T2 weighted images and b) T1 weighted images. Partial agenesis of corpus callosum – lack of genus, corpus is flatted.**



was PVL in 67 (51.3%) patients, with the highest proportion in the diplegic CP. In this study, PVL in MRI was observed in a similar proportion in preterm 11 (24.4%) and term 9 (20.0%) children with tetraplegia (data are not shown). On the other hand, 21 (52.5%) preterm children with spastic diplegia had PVL in MRI. Only 9 (20.4%) term patients with spastic diplegia had PVL. The patients with hemiplegia had a similar proportion of PVL in MRI. Porencephalic cysts were evident in 16 (12.4%) patients. Of the 16 cysts, 4 (8.7%) were present in patients with spastic tetraplegia, 2 (5.0%) in spastic diplegic children, and 10 (22.7%) in spastic hemiplegic children.

Cerebral atrophy was observed more often ($p<0.05$) in children with spastic tetraplegia 13 (28.3%) than in spastic diplegic patients 2 (5.0%). Three patients with spastic hemiplegia also had cerebral atrophy. Multicystic encephalomalacia lesions were found in 2 (4.5%) patients with spastic tetraplegia and with spastic hemiplegia. Congenital anomalies were evident in 15 (10.7%) children with CP. An open-lip schizencephaly was found in two children with spastic tetraplegia and in one patient with spastic hemiplegia. Close-lip schizencephaly was found in one child with spastic hemiplegia and spastic diplegia. Similarly agenesis of the corpus callosum was observed in two patients with tetraplegia *(Fig. 1)*. Holoprosencephaly was detected in one child with spastic tetraplegia and in one with spastic diplegia. Lissencephaly was found in two patients with tetraplegia. Almost all congenital lesions were found in children with epilepsy. Some patients had multiple lesions revealed on MRI. For example two preterm born children with spastic CP had PVL and congenital anomalies. Four patients with spastic tetraplegia had PVL and lesions in the basal ganglia and hippocampus. In this study we present only the main findings from MRI .

DISCUSSION

In this study we have demonstrated significant abnormalities on MRI in 95.3% of children with spastic CP. Our results are slightly higher but comparable with earlier reports [5,24,25]. The findings were heterogeneous in the spastic tetraplegic and hemiplegic CP children. Patients with spastic diplegia constituted a rather homogenous group. Preterm-type brain injury, especially PVL, dominated in this group. Other MRI findings were rare. Our results are in agreement with other authors who have reported that PVL is the main lesion in patients with spastic diplegia [5,8,26,27]. PVL is a form of hypoxic-ischemic damage typical of the immature brain and most commonly seen as a complication of preterm birth. As this lesion was found in children born at term it was considered to reflect a cerebral injury that had occurred in utero. Cerebral maldevelopment, due to a very early intrauterine lesion [cortical-/subcortical lesions] are also considered to be of major importance in diplegia and tetraplegia [5,18,25].

In our report, the most common finding on MRI was PVL in the patients with CP, the proportions of which were similar in the tetraplegic CP and the hemiplegic CP groups. PVL was observed more frequently in patients with spastic diplegia. PVL is a specific condition which refers to cell death of the white matter behind and to the side of the lateral ventricles due generally to a combination of decreased blood flow to the brain and reduced oxygen in the blood. It is important to note that almost half the CP children with PVL were born at term with no history suggestive of perinatal asphyxia and low birth weight.

Ventricular enlargement is common in preterm and low-birth-weight infants; indeed, one study observed it in up to 76% of very preterm infants who received an MRI scan during the first 48h of life [28]. In our study, ventricular enlargement was more often observed in children with spastic tetraplegia and preterm subjects who as babies had experienced periventricular hemorrhage of grade III or IV. This is in accordance with previous reports [26,29,30].

In children with spastic tetraplegia, PVL, cerebral atrophy and congenital were the most frequent abnormalities in the present study. In contrast to earlier reports [5,8] congenital anomalies were detected only in 13.3% patients with tetraplegic CP. Okumura *et al*., [27] reported brain anomalies in 22.2% of tetraplegic patients, and Kwong *et al*., [5] observed congenital brain anomalies in 42% of children with tetraplegia. On the other hand, her study group of patients with tetraplegia was not large (18 children). As a generality, children with spastic syndromes often show white matter injury, whereas extrapyramidal syndromes frequently have basal ganglia abnormalities on imaging [31]. However, in these syndromes, differential diagnosis is often broad, including a number of recognizable genetic and acquired disorders. Malformations of the central nervous system (CNS) may be isolated or appear as part of a genetic syndrome [32]. In the past few years there have been great advances in identifying the genes and genetic alterations for many isolated CNS malformations and syndromes with CNS malformations. Migration of post-mitotic neurons from the ventricular zone to form the cortical plate comprises one of the most critical stages in brain development.

Abnormalities (e.g. thinning or agesnis) in corpus callosum has been detected in children born very preterm, mental

retardation, autism, infantile spasms, and craniosynostosis. One of the most common brain abnormalities in individuals born very preterm is thinning of the corpus callosum, particularly of the posterior body (splenium) [1,10,15]. Damage to the corpus callosum during development has been found to be associated with poor neurological outcome and neuropsychological performance. The preterm children with CP have significantly smaller mean corpus callosum areas compared with the preterms who did not develop CP. However, the preterms born without CP also had significantly smaller body, posterior, and total corpus callosum areas compared with term-born controls. There is a strong association between the size of the corpus callosum and motor function in preterm children, investigated at school age. A poorer score on the Movement Assessment Battery for Children is related to a smaller corpus callosum. On the other hand, a larger corpus callosum was strongly associated with better Test of Visual Motor Integration standard scores [33].

Schizencephaly is a neuronal migration disorder characterized by gray-matter-lined clefts extending from the pial surface to the lateral ventricles [34,35]. The clinical features of schizencephaly are extremely variable and their severity is closely related to the importance of the cleft. Children with unilateral schizencephaly present hemiparesis and mild mental delay [34]. Children with bilateral cleft are tetraparetic with severe mental deficits. Schizencephaly was noted in previous reports on MRI in patients with CP [8,18]. In the present study, we also found five children with schizencephaly among the patients with spastic CP.

Lissencephaly is a brain malformation known as 'smooth-brain', characterized by a smooth or nearly smooth cerebral surface. It encompasses a spectrum of gyral malformations from complete agyria (absent gyri) to regional pachygyria (broad gyri), and merges with subcortical band heterotopia [36]. Five genes that cause or contribute to human lissencephaly, including *LIS1*, *14-3-3*, *DCX*, *RELN* and *ARX* have been documented [37].

Polymicrogyria is a brain malformation due to abnormal cortical organization, in which the brain surface is irregular and the normal gyral pattern is replaced by multiple small, partly fused gyri separated by shallow sulci [38]. Two histological types, unlayered or four-layered, can be distinguished. Polymicrogyria is a rare manifestation of chromosome 22q11 deletion syndrome [39]. In this report, we noted two cases of polymicrogyria of patients with spastic hemiplegia. These patients also had epilepsy with a good response to antiepileptic drugs. Moreover, all children with congenital anomalies in this study had epilepsy.

Holoprosencephaly is classified into four types (alobar, semilobar, lobar holoprosencephaly, and syntelencephaly) [40]. In our study, two patients had lobar holoprosencephaly in the posterior frontal and parietal regions of brain.

Our findings are in accordance with previous clinical and neuroradiological reports on CP [4,5,8,12]. 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 to detect brain abnormalities such as PVL, cerebral atrophy or porencephaly. Furthermore, it is vital to distinguish brain malformations from pre- or perinatal brain injury. Early detection of brain abnormalities in children with CP may help in the prognosis and in the introduction of appropriate therapy (rehabilitation of motor impairment or language therapy).

This report has some limitations, such as the absence of a control group and lack of genetic studies of patients with brain malformations.

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