

Developmental disorder – an early sign of cerebral palsy

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Abstract

Background. Cerebral palsy is one of the most important causes of disability in children. Intensive rehabilitation in cerebral palsy is personalized in accord with the deficits, activity limitations and participation restrictions, but an early etiologic and clinical diagnosis in a multidisciplinary approach, to differentiate cerebral palsy from other causes of neurodevelopmental disorders, is required to direct the pharmacological approach and prognosis.

Aims. This paper presents the first study on a Romanian population in terms of the most relevant cerebral palsy risk factors and their relation to the age when cerebral palsy was diagnosed, aiming to support a possible early diagnosis prediction model.

Method. Retrospective study conducted on a group of 320 children diagnosed with developmental disorder admitted to the Department for Children Neuro-Psychomotor Rehabilitation of the Psychiatry Hospital in Sibiu during 2015-2018.

Results. The number of neurodevelopmental disorders generated by cerebral palsy in the examined group is relatively small (11.56%). The highest proportion of neurodevelopmental disorders in children with cerebral palsy (according to the subsequent diagnosis) was seen in children born under 30 weeks of pregnancy, exhibiting perinatal intracranial hemorrhage and displaying increased muscle tone and seizures.

Conclusions. The study establishes correlations between the variables assessed, which may point to a formula for predicting the diagnosis of cerebral palsy in children initially examined for a developmental disorder.

Keywords: cerebral palsy (CP), neurodevelopmental disorder (NDD), disability, predictor.

Introduction

With a prevalence between 1.3 and 4.4 per 1,000 live births since 1980 (Johnson, 2002), cerebral palsy (CP) is the most common cause of childhood disability worldwide, affecting not only the underdeveloped countries but also the developed nations (prevalence of 2 to 2.5 per 1,000 live births) (***, 2017). These numbers serve as a rough guide only, as CP is underdiagnosed and underreported (in the EU, 21 Member States report cases to the EU Commission - Surveillance of Cerebral Palsy in Europe) (Sellier et al., 2016). The disability degree determined by CP is extremely varied. The dysfunction impairs the sensitive-sensory and motor functionality, also the cognitive functionality, in some cases, and results in a reduced level of activity and significant participation restrictions, a terrible burden on the family and the community as a whole, and a low quality of life for both the diagnosed child and their caregivers. Medical rehabilitation interventions are based on a multidisciplinary assessment and enhance the CP children's quality of life (Tsoi et al., 2012). Physical medicine and rehabilitation

interventions must be carefully tailored according to the level of functional impairment established by specific areas and the patient's reluctance and abilities (Balci, 2016).

Neurodevelopmental disorders (NDDs) is an umbrella term comprising disorders usually diagnosed in childhood, less commonly in adolescence. NDD reunites manifestations such as: cognitive disorders (including communication and social skills), sensory-based motor disorders and coordination disorders of various origins (***, 2013).

Cerebral palsy manifests by non-progressive movement disorders characterized by inadequate neurological control of movement and posture due to brain insults which act pre-, intra-, or postnatally in the early years of life (Spence & Sheffer, 2020). Motor impairment is a mandatory criterion and may or may not be accompanied by mental retardation, epilepsy, sensory deficiencies, cognitive and behavioral disorders. The clinical picture divides CP into four main types: 77% of the cases display spastic CP, 5% display dyskinetic CP, 3% display ataxic CP, and 15% display mixed forms of CP (***, 2022).

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The differential diagnosis from other conditions classified as developmental disorders - global developmental delay, autism spectrum disorders, intellectual disabilities, developmental coordination disorders, neurogenic genetic disorders, neurotoxic disorders and so on (Morris-Rosendahl & Crocq, 2020) is a challenge because of the clinical picture with many common symptoms, which also change over time. These changes are triggered, among others, by the growth and development processes, along with the intensive and sustained rehabilitation intervention, which must be initiated as early as possible, even in the absence of the differential diagnosis, to avoid complications and to improve the patients' functional condition. 74% of all CP cases are also accompanied by other DD comorbidities (Francés, 2020). The CP diagnosis is usually made around the age of 3 or 4 years old, the developmental disorder being the red flag that brings the family to the doctor, sometimes long before the differential diagnosis is possible (Corporate Author, 2000). The differential diagnosis is difficult but can be highly important, especially when DDs are caused by metabolic diseases, which, once diagnosed, can be specifically targeted, with a substantial improvement of the patient's condition.

The etiology of cerebral palsy may be shared with the etiological or contributing conditions of other DD-generating pathologies. The risk factors for CP are indeed numerous and include a variety of prenatal and perinatal conditions, along with the gestational age at birth and the newborn's weight. These are supplemented by postnatal causes (Reddihough & Collins, 2003). This whole clinical picture is difficult to create without a highly detailed medical history, but there is some important data that can guide the doctor in pediatric rehabilitation towards the CP diagnosis, supporting an early diagnosis, even in the absence of special technological means. Accessing high resolution and specificity investigations is still costly (both financially and in terms of time), which is why a formula to guide the practitioner during the differential diagnosis while making use of the anamnestic and clinical data could be useful.

The Department for Children Neuro-Psychomotor Rehabilitation of the Psychiatry Hospital in Sibiu attends to children both from the entire Sibiu County and from other counties in the country as well. Many of the admitted children display DD. During the data collection process as part of a large retrospective study, it was found that some of the children later returned to the hospital with a different diagnosis, which, in some cases, stated infantile cerebral palsy.

The current study aims to assess whether and to what extent children with perinatal distress and originally diagnosed with DD display DD as part of CP, subsequently diagnosed as such, being the first study of its kind on the population with CP in Romania.

Hypothesis

The number of children displaying DD and subsequently diagnosed with CP is small compared to the total number of children diagnosed with DD. There are common contributing factors for DD (regardless of the general DD pathology), of which: prematurity, a low Apgar score, neonatal seizures and intracranial hemorrhage at birth, and the association of

these factors may help predict the CP diagnosis as NDD-generating pathology.

Material and methods

Research protocol. Retrospective observational study.

a) *Period and place of the research*

The Department for Pediatric Recovery of the Psychiatry Hospital in Sibiu, during 2015-2018.

b) *Subjects and groups*

The study was conducted on a group of 320 children diagnosed with developmental disorder. In 37 cases, the children were subsequently readmitted with a diagnosis of CP; the others either did not return (did NDD conditions improve?) or had other diagnoses. In what follows, we shall call CP patients the subjects diagnosed with CP following their NDD diagnosis. We shall call NDD patients the subjects whose DD diagnosis was confirmed on the second admission. The data were anonymously extracted from the observation charts. The parents of the children gave their consent for children to participate in non-experimental scientific research when admitted in the hospital.

c) *Applied tests*

The study is retrospective, involves only processing data from the medical sheets. The variables analyzed were: gestational age, Apgar score, neonatal seizures and presence of intracranial hemorrhage at birth. Muscle tone disorders were taken into account from the clinical picture.

d) *Statistical processing*

The following statistical methods were used (with the aid of the R programming language, version 3.6.2):

- To compare percentages, the chi-squared test (or its equivalent, Fisher's exact test, when the approximation or generalization to a larger sample performed by the chi-squared test was not possible) was used to see whether the differences in proportions were significant from one level of the categorical variable to another. A p-value under the 0.05 threshold indicates a significant difference.

- To compare the numerical values from one group of patients to another, as independent groups, either the t-test was used if the values were normally distributed, or the Wilcoxon-Mann-Whitney test was used if the values were abnormally distributed and/or if they were ordinal. Again, a p-value under the 0.05 threshold indicates a significant difference.

- To predict the likelihood that patients initially diagnosed with DD would later receive a CP diagnosis, the logistic regression model or logit model was used. Again, where an entry or interdependent variable displayed a p-value lower than the 0.05 threshold, it was deemed relevant.

Results

At first, the group of children with DD and the group of children with CP who were initially diagnosed with DD were compared in terms of variables: gender, residence and background to determine whether there are statistically relevant differences.

Of the 320 patients initially diagnosed with DD, about 56% were male. From a statistical point of view, this difference (gender distribution) is still significant, yet close to the 0.05 threshold: X-squared = 4.5125, p-value = 0.03365 according to the chi-squared test.

A study documenting the diseases possibly afflicting the development of children (developmental disabilities) and targeting 195 countries and territories shows similar statistics: 54% of the children aged 5 or less included in the study are male (Olusanya et al., 2018). There is a high addressability from other counties of the country (possibly due to the location in the center of the country), 2/3 of them come from outside Sibiu County. Nearly 2/3 come from urban areas, i.e. 61%, which may be explained either by the greater awareness of parents or family doctors in the urban areas, or by a greater accessibility to health services, or both.

Of the criteria that may be relevant by association, we looked at residence, background and the age at which the children with DD who were subsequently diagnosed with CP presented for rehabilitation treatments.

The patients who underwent the transition from DD to CP mostly came from other counties. The percentage or distribution difference was highly statistically relevant in this case as well: X-squared = 42.378, p-value = 7.522e-11. These results were generated by the test of proportion.

As far as the background variable is concerned, for the group of patients with CP, the results or frequency difference was again significantly different between the rural and urban areas: X-squared = 7.7838, p-value = 0.005272.

Patients whose diagnosis was changed from DD to CP

In terms of age, the situation of the 37 cases that were initially admitted with a diagnosis of DD and at variable time periods were diagnosed with CP, is shown in Figure 1, where the age is expressed in months (from 0 to 70 months).

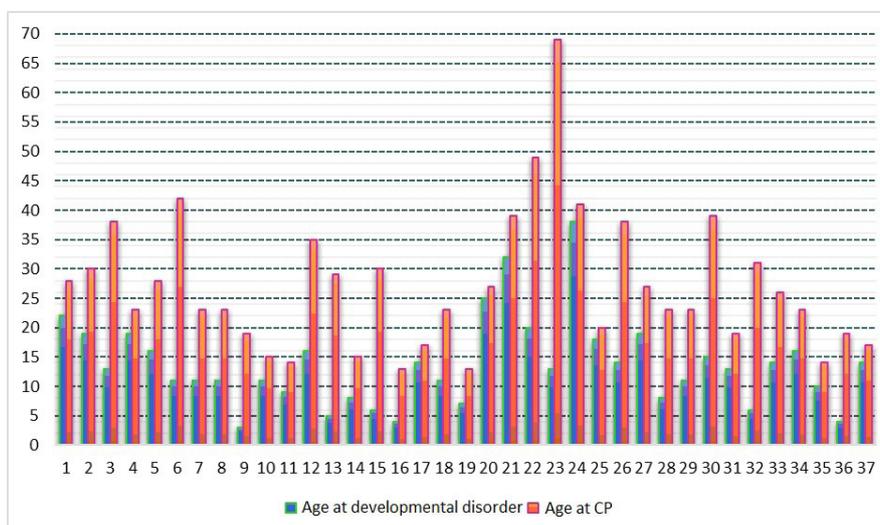
As seen in Fig. 1, the time period between the two diagnoses varies randomly; the data analyzed does not indicate any correlation between the age at which the patient originally presents and the age at which CP is diagnosed. The time difference may be attributed to several factors: perinatal distress, clinical picture, presence of comorbidities, follow-up or not of the rehabilitation program after discharge.

Early intervention is of utmost importance, as one of the factors improving the chances to decrease the disability

degree in children with CP is early assessment that detects the developmental disorder and allows the early initiation of complex and tailored rehabilitation therapy, including resorting to advanced technological means to foster rehabilitation (robotic therapy and serious gaming) and given the comorbidities of CP (including epilepsy, impairment of cognition, vision, hearing, and disturbances of growth and gastrointestinal function) and the specific complications of CP - defective development of the musculoskeletal system, osteoporosis, fractures, infections, incidental cognitive deficiencies (Gulati & Sondhi, 2018). Early rehabilitation intervention can significantly improve a child's psychomotor abilities and enhance their quality of life (Burdea et al., 2013).

For the therapeutic intervention to be successful in terms of stimulating neuroplasticity, the therapeutic window for CP basically comprises the first 4 months of life, with the birth being a reference point and considering the perinatal period and the time of the insult (brain injury). Therefore, establishing an early diagnosis protocol for CP is mandatory. In 2000, the recommendations of the SCPE network established a time period for a positive CP diagnosis of up to 4 years of age (Corporate Author, 2000).

In our department the age criterion represents a priority for admission, but the addressability is not always direct, i.e. not all newly admitted cases come to us in the first instance, but are referred by other specialists. This explains the large variability of situations when analyzing the group according to the age criterion. To that effect, the time period between the first admission when the child was first examined for DD, and the first admission when the same child returns with a diagnosis of CP is variable. For example, case no. 37, where the first admission with the DD diagnosis occurred at 14 months of age (1 year 2 months old), and the following admission occurred three months later, with the CP diagnosis. Case no. 6, the first admission with the DD diagnosis occurred at 11 months of age, and the admission with the CP diagnosis, at 42 months of age (3 years 6 months old).



Legend: 0-70 = age in months; 1-37 = case index; blue = age upon first hospital admission, magenta = age upon cerebral palsy diagnosis. Fig. 1 – Age/diagnosis.

Of a total of 320 patients with developmental disorder only 37 were found on subsequent admissions with a diagnosis of CP; the proportion of children with a diagnosis of CP who returned for admission after initially presenting with a diagnosis of DD equaled 11.56% of all patients initially presenting with DD.

Relationship between the CP diagnosis and the relevant risk factors

The relationship of these pathologies with the common perinatal factors, namely: a low gestational age, a low Apgar score, presence of intracranial hemorrhage and neonatal seizures, and increased muscle tone, is analyzed below.

1. Gestational age

A normal pregnancy lasts for 38 to 40 weeks. Prematurity affects 11% of all live births in the world (Walani, 2020). Over the last decade, advances in modern medicine have led to increased survival rates for babies born at ever younger gestational ages. Depending on the gestational age, premature births are classified as follows: under 28 weeks – extremely preterm, 28 to 32 weeks – very preterm, 32 to 34 weeks – moderately preterm and 34 to 36 weeks – late preterm. An important indicator is the survival rate which has progressively increased to 50%-70% for extremely premature newborns (under 28 weeks) (Glass et al., 2015).

For the group of DD patients, the distribution by gestational age is shown in Fig. 2, where the percentage of preterm births exceeds the percentage of term births. Very preterm accounts for 10.95%, moderately and late preterm for 40.99%, and term births for 48.06%.

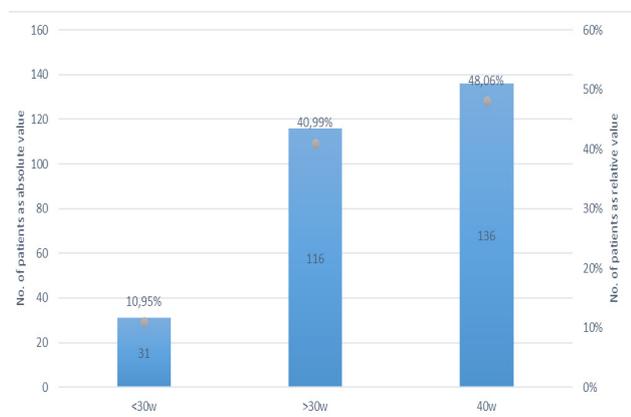


Fig. 2 – Gestational age for DD patients (w = no. of pregnancy weeks).

The gestational age for the group of patients who developed CP is not statistically different from those with DD, the group of births under 30 weeks however registering a higher percentage, 16.22% of the total, as shown in Fig. 3.

Extremely preterm is one of the conditions contributing to the appearance of neurological sequelae or severe pathologies leading to disability in survivors. The data collected shows that the percentage of preterm births in children with CP in the examined group is only slightly higher than the percentage of preterm births for DD patients, which is statistically irrelevant. The result

confirms the data in the medical literature (Granild-Jensen, 2015). The prevalence of CP in preterm infants is 40 times higher than in term infants worldwide, with a normal birth weight (Krägeloh-Mann & Cans, 2009).

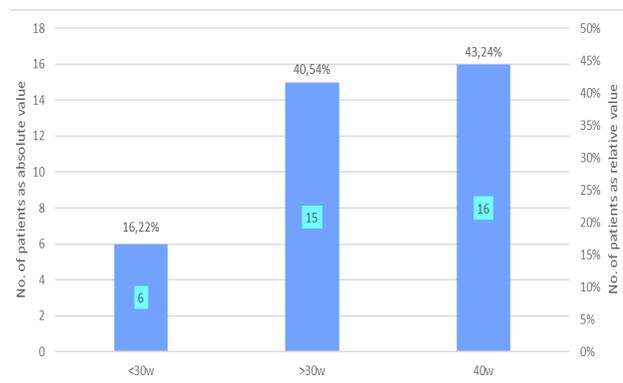


Fig. 3 – Gestational age for CP patients.

2. Apgar score

The vitality score for newborns – Apgar – with values ranging from 0 to 10, at five and ten minutes after birth, is currently acknowledged as a predictor for CP (Persson, 2018). In the initial DD group, an Apgar score lower than 4 is rarely encountered (approximately 6%), most children scoring 9 (31.80%) and 10 (26.86%).

In the group of children diagnosed with CP, the low Apgar score prevailed; the percentage of the values of 4 and lower is 35.13%, of which 16.22% had Apgar 1.

The CP and DD children displayed a statistically relevant difference: from a median Apgar score of 6 (mean of 5.459) to one of 9 (mean of 8.226): $W = 2228.5$, $p\text{-value} = 5.923e-09$ (Wilcoxon-Mann-Whitney test).

3. Neonatal seizures

In preterm infants, neonatal seizures are frequently associated with intracranial hemorrhage, cerebral ischemia, infections of the central nervous system and serious neurodevelopmental manifestations (Vegda et al., 2022).

Of a total of 320 patients, 25 suffered neonatal seizures (7.81%). Of the 25 patients, 11, i.e. 44%, were diagnosed with CP. Of the 283 patients diagnosed with DD, only 26, i.e. 8.81%, suffered neonatal seizures. This proves that a rather high percentage of the patients suffering seizures, 44%, respectively, were subsequently diagnosed with CP. This difference is statistically relevant (Fisher's exact test): $p\text{-value} = 1.604e-05$.

4. Intracranial hemorrhage

Intracranial hemorrhage is frequently associated with a low Apgar score and neonatal seizures even in term newborns (Hong & Lee, 2018). Our study did not consider the varying degrees of severity of intracranial hemorrhage but only its presence in the birth history.

Of a total of 283 children with DD, a percentage of 18.73% displayed intracerebral hemorrhage at birth. For the CP children, hemorrhage is present to a much higher degree, 43.24%, respectively. Statistically, there is a difference between the percentage of those who developed CP among those with hemorrhage versus those without hemorrhage. In other words, 23.19% (16 out of 69) is significantly different from 8.37% (21 out of 251).

5. Muscle tone

In the clinical picture of both the developmental disorder (DD) and CP, a highly important element is muscle tone with its disorders (increasing = hypertonia, or decreasing = hypotonia). In the children with DD, tone variations were found in 260 cases out of 283 and, of those who returned with a diagnosis of CP, all 37 had muscle tone disorder. Of those with muscle hypertonia found upon the original admission, 38.27% (i.e. 31 out of 81) subsequently developed CP. In the children with hypotonia, only 2.78% subsequently return with CP. This difference is statistically relevant (i.e. the hypothesis that we had the same conversion percentages for each of the three muscle tone categories can be dismissed), with a *p-value* of $9.197e-15$ for Fisher's exact test.

Correlations between the variables considered – can a CP diagnosis be predicted for the DD children?

The study aims to establish correlations between the variables assessed that would lead to a formula for predicting a CP diagnosis in children initially presenting for developmental disorder.

The following chart comprises data about neonatal seizures, intracranial hemorrhage, and the Apgar score for the group of DD patients, in correlation.

It is noticed that 21.43% of the children suffering neonatal seizures also displayed intracranial hemorrhage. The remaining 78.57% did not display intracranial hemorrhage. The mean Apgar score was 7.

Of the children not suffering neonatal seizures, 50 (18.59%) displayed hemorrhage, with the remaining 219 (81.41%) not suffering seizures or displaying intracranial hemorrhage, with an Apgar score over 8 (Fig. 4).

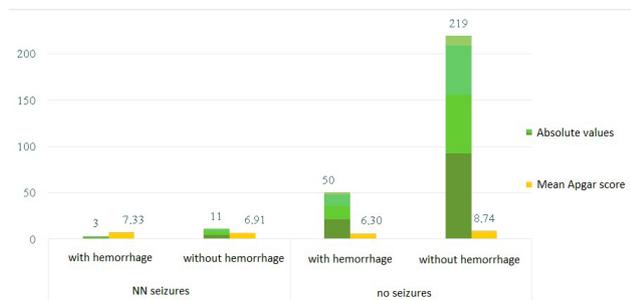


Fig. 4 – Distribution of DD patients by NN seizures, intracranial hemorrhage, and Apgar score.

As seen in Fig. 5, in the CP group, 29.73% suffered neonatal seizures at birth, of which 54.55% also displayed intracranial hemorrhage and a low Apgar score mean - 5. Of the remaining 70.26% who did not suffer seizures at birth, 38.46% had intracranial hemorrhage, associating a medium Apgar score - 6.

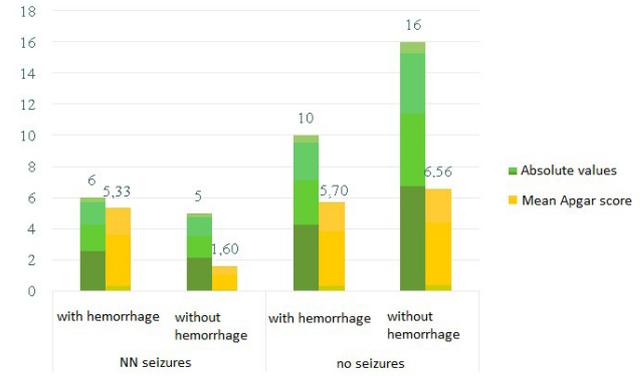


Fig. 5 – Distribution of CP patients by NN seizures, intracranial hemorrhage, and Apgar score.

The low Apgar score, accompanying the intracranial hemorrhage and seizures, is documented in the medical literature as well (Hong & Lee, 2018).

We notice in Table I, below, that, if we want to incorporate all the relevant variables into a single prediction model, to see how they interact and to assess the extent to which, combined, they can predict the transformation of the diagnosis of developmental disorders into infantile cerebral palsy, although on the individual level (see the separate analysis above), we have identified several aspects, in interaction we are mainly talking about:

- A low Apgar score;
- Muscle tone, namely hypertonia.

The interpretation is always based on the baseline value for each of the categorical variables involved, invalidating the null hypothesis:

- Apgar score: being a numerical variable, the interpretation is made as for any linear regression, meaning: for every extra unit of Apgar score, the odds ratio of conversion versus no conversion in CP equals 0.76 or $exp(-0.2781)$ (i.e. 24% lower). The 0 to 4 score, present in 35.13% of the CP cases in the examined group, indicates in itself a high risk of CP.

Table I
Invalidating the null hypothesis.

Coefficients	Estimate	Std. Error	z value	Pr (> z)
(Intercept)	1.5655	0.8278	1.891	0.05860
gestational_age >30w	0.4835	0.6930	0.698	0.48538
gestational_age 40w	1.1181	0.7965	1.404	0.1604
APGAR score	-0.2781	0.0907	-3.066	0.00217 **
muscle_tone decreased	-2.4939	0.5047	-4.941	7.77e-07 ***
muscle_tone normal	-17.7787	1289.1073	-0.014	0.989
NN_seizures no	-0.7179	0.6423	-1.118	0.26372
intracranial_hemorrhage no	-0.6052	0.5124	-1.181	0.23754

(- = value under the 0.05 threshold (see last column).)

- Muscle tone (hypotonia): the odds ratio (here the missing baseline value is hypertonia) for those with hypotonia versus those with hypertonia for undergoing conversion equals 0.08 or $\exp(-2.4939)$ (so 92% lower odds for developing CP in those with hypotonia versus those with hypertonia). Basically, the patients with CP displayed hypertonia (most likely of central neurological origin) in 83.7% of the cases, similar to the percentage provided by studies in other states (80%) (Hägglund, 2021).

Table I below comprises the detailed variables, and their statistical relevance.

Discussion

The relevance of the variables considered is obvious, similar to the one established worldwide (Gururaj et al., 2003; Parody et al., 2020). The most important association as a predictor of CP is represented by a low Apgar score accompanied by hypertonia. The range of risk variables is wider, and an accurate diagnosis of CP currently requires investigations that are difficult to access (genetic tests) and that are difficult or even highly risky for some patients (brain MRI) (Himmelmann, 2017). Establishing a complex diagnostic algorithm could be very useful. The SCPE Collaborative Group of the EU Commission proposes a guiding definition of CP: “Cerebral Palsy (CP) is a group disorders involving movement and posture and of motor function; it is permanent, but not unchanging; it is due to a non-progressive interference, lesion, or abnormality of the developing/immature brain. This definition specifically excludes progressive disorders of motor function, defined as loss of previously acquired skills in the first 5 years of life” (Corporate Author, 2000). SCPE also proposes a decision tree for the diagnosis of CP, but it only includes the differential diagnosis for conditions with motor impairment of non-central origin and the differential diagnosis for conditions with chromosomal impairment.

In the given situation, the time period required to establish the diagnosis of CP according to the SCPE can and should be used for the early therapeutic intervention. Thus, it would be useful to develop a program in which therapy indicated by a suggestive clinical picture would be initiated before 4 months of age, followed by a follow-up scheme with short deadlines for the infant and toddler, reuniting all professionals involved in the diagnosis and therapy, i.e. the therapeutic team: the neonatologist, neurologist, pediatric rehabilitation doctor, ophthalmologist, ENT specialist, pediatrician, family doctor, psychologist, and the physiotherapist (***, 2011).

There is a proposition for a follow-up program for the newborns at risk initiated in Sibiu, which unfortunately misses the rehabilitation team, namely the rehabilitation doctor and the physiotherapist.

The early diagnosis of CP is essential for several reasons: it enables the early therapeutic intervention that leads to learning motor patterns as close to normal as possible, it increases the cognitive ability, it prevents complications (hip dislocation, scoliosis, osteoporosis, muscle contractures leading to joint deformities) and, last but not least, it helps the parent to overcome the depression caused by insecurity once they are included into therapy (Novak et al., 2017).

Conclusions

1. The number of DDs generated by CP in the examined group is relatively small (11.56%).
2. The highest proportion of DD children with CP (according to the subsequent diagnosis) was seen in children born under 30 weeks of pregnancy (16.22%).
3. Neonatal seizures occupy a large percentage (44.00%) in the medical history of the children displaying developmental disorder in the context of CP subsequently diagnosed.
4. Intracranial hemorrhage occurring at birth increases the DD prevalence because of CP.
5. An increased muscle tone is an alarm signal – it indicates a high probability of CP.
6. Even if the rehabilitation therapy is instituted with the first functional diagnosis of DD, it is necessary to have a diagnosis of CP as early as possible based on certain variables included in a standardized assessment protocol, in order to establish/continue an intensive and tailored program to stimulate the child’s normal development and/or recovery of functional deficiencies and to avoid the worsening of sequelae.
7. Our study establishes correlations between the assessed variables, which may lead to a formula for predicting the CP diagnosis in children initially presenting with developmental disorder.

Conflict of interests

The authors declare no conflict of interests.

Acknowledgments

This study represents partial results of a larger retrospective study to be included in the doctoral thesis of the first author.

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