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The predictive value of 'red flags' as milestones of psychomotor development of premature babies – preliminary study

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Abstract

Introduction. Premature babies are a special group at risk of persistent brain damage caused by diseases, the most serious of which are cerebral palsy(CP), autism spectrum disorders (ASD) and mental retardation, among others. These conditions may occur concurrently, but appear more often as separate disease syndromes in the same group of at-risk children. Long-term observation of psychomotor development by an interdisciplinary medical team closely cooperating with parents is necessary. It is important to detect the risk of developing these diseases as soon as possible in all development spheres.

Materials and method. The research was conducted to demonstrate the prognostic value of 'red flags' of developmental milestones and the ability to detect early signs of risk of developing CP and ASD in extremely premature babies. In this preliminary study, 42 preterm babies, born after less than 32 weeks pregnancy participated.

Results. The occurrence of ‚red flags'in the spheres: gross motor, fine motor and cognitive at 9 months was strongly associated with their presence at 24 months. The sensitivity and specificity were: gross motor – 0.91 (95% CI: 0.59, 1.00) and 0.94 (95% CI: 0.79, 0.99); fine motor – 0.83 (95% CI 0.36–1.00) and 1.00 (95% CI: 0.90–1.00); cognitive – 1.00 (0.40, 1.00) and 0.97 (0.86, 1.00). Other spheres had lower sensitivity but high specificity.

Conclusions. The conclusion is that the ‚red flags'at the 9 months milestones already predict the normal or developmental delay of premature babies, and predict the risk of CP and ASD. Due to the availability and lack of the need for specialized and costly training, it is worth considering their use in everyday life medical practice.

Key words

milestones, psycho-motor development, alarm symptoms, prognosis, premature babies

INTRODUCTION

It is known that about 10% of children from the 'risk group' of premature babies born in asphyxia or with other pathological conditions, may occur developmental disorders [1, 2, 3, 4, 5]. Therefore, they should be included from birth in the monitoring programme for early identification and treatment of developmental disorders [6, 7, 8, 9]. Although the evidence for the effectiveness of therapeutic tools is inconclusive, it is recommended to take action during infancy. Increased brain plasticity and 'critical windows' for the development of individual sensory functions and skills justify this approach [10, 11, 12]. Premature babies are a special group at risk of persistent brain damage; the most serious of which are cerebral palsy (CP), autism spectrum disorders (ASD) and mental retardation, among others [13, 14, 15]. These conditions may occur concurrently, but more often they appear as separate disease syndromes in the same group of at-risk children [16]. Long-term observation of psychomotor development by an interdisciplinary medical team closely cooperating with parents is necessary [17]. In the first half year of life, movement disorders are the easiest to recognize. Symptoms of abnormal speech development, cognitive and socio-emotional functions usually appear in the second half of the first year, or later [18, 19]. The latter symptoms can be easily overlooked, especially when motor development is normal and the duration of developmental monitoring is too short.

Assessment of psychomotor development using 'milestones' is widely known and practiced. Usually, the time interval and age at which the child achieves ability is described, although it is not always clear when individual achievements should be considered delayed [20]. The current research uses the study by Cara F. Dosman et al. [21] where developmental achievements are assigned to the 90th percentile, i.e., age by which 90% of children have mastered a certain skill. Lack of skills is defined as so-called 'red flags' (RFs). Failure to reach

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a given milestone in a given time usually indicates a delay and requires further action. Development milestones have been selected based on scientific evidence and formulated for children up to 60 months of age (5 years). The skills are divided into groups: gross motor (GM-S), fine motor including self-care (FM-S), communication – speech, language and nonverbal (COM), cognitive (COG) and social-emotional area (SO-EM) [21]. This assessment method has been used by the study authors in clinical practice in the children's rehabilitation centre since 2014 to monitor the development of premature babies, children born in asphyxia, and other infants at risk of abnormal development. A research programme was carried out, the results of which are presented in this study.

OBJECTIVE

The research was carried out to show that monitoring psychomotor development with evidence-based milestones allows the detection of early signs of risk of developing CP and ASD in extreme premature babies. The aim of the study was to determine the prognostic value of milestones at the age of 9 months, in relation to the neurodevelopmental outcome at the age of 2 years. Disorders were assessed in all sectors of psychomotor development.

MATERIAL AND METHOD

Extremely premature babies who were monitored for psychomotor development during the first 2 years were enrolled. The study group was formed from among all premature babies who came to the rehabilitation centre within 12 months (n=196 children), extreme premature babies (n=58 children), i.e. children born before the 32nd week of pregnancy. This limitation was aimed at observing the group at the highest risk of developmental disorders. Next, monitoring of psychomotor development was carried out.

The study at the age of 9 months of corrected age (9M-CA) and 24 months of real age (24M-RA) was carried out in all children according to the developed scheme. Unified study cards were used that included 'red flags' (RFs) for evidence-based milestone ages (Fig. 1) [21]. The rehabilitation doctor examined 58 children, but only 42 had full documentation and parental consent; therefore, the statistical analysis concerned only this number (n=42, 21 boys and 21 girls).

Methodology. Assessment of the children was carried out by a rehabilitation doctor at 9M-CA and 24M-RA, using evidence-based milestones in 5 developmental spheres: GM-S, FM-S, COM, COG, SO-EM. The occurrence of alarm symptoms, so-called 'red flags' (RFs'+') in the spheres listed above was marked when the child did not perform the described skills at 9 or 24 months. If the child had the correct skills described for 9 and 24 months of age in these areas of development, they were labeled as absence of red flags (RFs'-').

Parents of children with RFs'+' present in the final study (24M-RA) were asked to complete the Modified Autism for Young Children (M-CHAT) checklist available on www.badada.pl. Thanks to the completed questionnaires, it was possible to determine the risk of autism spectrum disorder (ASD) in the study group. In addition, all children aged 2 years were examined by a paediatric neurologist who confirmed or excluded cerebral palsy.

The rehabilitation doctor's examination also included an assessment of posture, gait pattern, presence of selective limb movements, and spasticity testing. However, they were not subject to research analysis.

Based on the medical documentation of the rehabilitation centre, the second stage of research was conducted. The prognostic value of RFs present in 9M-CA month was checked in relation to the neurodevelopmental outcome and present RFs at the age of 2 years.

Statistics. Quantitative variables were characterized based on the average, standard deviation, minimum and maximum. The nominal variables are described by means of cardinality and percentage. Relationships between nominal variables were evaluated using the Chi2 test with the Yates correction for independent variables and the McNemar test for dependent variables. The accuracy of the test was demonstrated by sensitivity and specificity. The positive predictive value and the negative predictive value of the test were also calculated. All results were presented with a 95% confidence interval (95% CI). Statistical analysis was carried out in the *Statistica* programme (StatSoft Polska, 2018).

RESULTS

Patients. In the examined group of 42 children the average gestational age was 29±1.7 weeks. The average Apgar score in the 1st minute was 5.6±1.9 points, and in the 10th minute – 7.6±1.3 points. The birth weight of the child was on average 1,232±305 grams. Ultrasound examination of the brain (cUS) at delivery revealed abnormalities in 15 children (35.7%) (Tab. 1.)

Table 1. Characteristic of the studied group, n=42

		Average	Min.	Max.	SD
Gestational age (HBD)		29.17	25.00	31.00	1,70
Apgar (1st minute of life)		5.57	0.00	9.00	1,94
Apgar (10th minute of life)		7.62	4.00	10.00	1,29
Birth weight		1232	650	1780	305
cUS at the time of delivery	Correct, n (%)	27 (64.29%)			
	Incorrect, n (%)	15 (35.71%)			

Results of the neurodevelopmental outcome and 'red flags'. The neurodevelopmental outcome of children aged 2 years was conducted by a rehabilitation doctor. The number of children with normal development was 26 children (61.90%), with CP symptoms – 4 children (9.52%) and requiring further observation -12 (28.57%). Parents of all children in whom RFs+ were present in the final study (n=16) were asked to complete the M-CHAT survey (ASD screening tool). From among 12 children qualified for further observation, the results of the completed M-CHAT questionnaire for 3 children indicated the need for re-evaluation. In the CP-children, in one case the obtained result indicated the necessity of re-evaluation in the direction of ASD.

The number of children with the 'red flags' (RF+) present in the 9M-CA and the 24M-RA is shown in Table 2.

Examination cards: 9M-CA; 24M-RA		
First name and last name .... Age .... Weight		
Part 1		
Posture: symmetry / asymmetry of the body in sitting / standing position: yes / no (describe) .... Gait pattern (24M): normal/abnormal (describe) .... Hips: correct – no (describe) .... Selective movements: hands – yes / no; feet yes / no Spasticity (Tardieu scale): Upper extremity: no / yes: arm (left/Wright); forearm (left / right); wrist (left / right) Lower extremity: no / yes: hip adductors (left / right); knees (left / right); feet (left / right)		
Part 2 **'Red flags' of developmental milestones** (described by CF Dosman et al. [21])		
Sectors of development	9 months – child skills	24 months – child skills
Gross Motor (GM-S)	Postural reflexes present Rolls both ways Sits well	Runs, jump, kicks Throws ball overhand three feet forward Walks upstairs marking time, no railing
Fine Motor (FM-S)	Transfers Radial – digital grasp (thumb with 1st and 2nd fingers, no palm) Touches 'Cheerio' with finger Raking pincer grasp	Copies vertical line Stacks 6 cubes Uses spoon, helps dress
Speech-Language (COM)	Looks at familiar named object Vocalizes to initiate	50 words, two-word phrases Talks instead of gestures Nods 'yes', blows kisses, 'shh', 'high five' (representation) Speech 50% intelligible to strangers
Cognitive (COG)	Object permanence Explores caregiver's face Searches for hidden toy	Symbolic representation, simple pretend (toy broom, toy cup to self / doll, pushes car to work Strategies without rehearsal Tries to make toys work
Social-Emotional (SO-EM)	Attachment development established	Social referencing Comforts others (empathy) Joint attention: points to clarify word approximations Parallel play 'No', 'Mine'

Figure 1. Study cards

Table 2. Number of children with RF+ at 9M CA and 24M RA (n, %)

Present 'red flags' (RF+) in spheres:	9M-CA		24M-RA	
	n	%	N	%
Gross Motor (GM-S)	12	28.57	11	26.19
Fine Motor (FM-S)	5	11.90	6	14.29
Speech-Language (COM)	5	11.90	11	26.19
Cognitive (COG)	5	11.90	4	9.52
Social-Emotional (SO-EM)	3	7.14	7	16.67

Results of statistical analysis. The first stage of the analysis was assessment of the relationships between: (1) individual development dimensions in 9M-CA, (2) individual development dimensions in 24M-RA, (3) individual development dimensions in 24M-RA in relation to individual development dimensions in 9M-CA, (4) individual dimensions of development in 9M-CA and in 24M-RA in relation to the results of the brain ultrasound examinations. This allowed for a preliminary indication of the most important relationships between variables and avoiding the inclusion in the logistic models of variables strongly related to each other. (Fig. 2)

In the next stage, the sensitivity and specificity of RFs were determined for 5 developmental sectors. The positive predictive value was calculated, which indicated the probability of RFs in 24M-RA in children with RFs in 9M-CA in each developmental sector and negative predictive value, which meant the probability of no RFs in 24M-RA in children with no RFs present at 9M-CA. (Tab. 3).

GM-S. The sensitivity and specificity of the presence of RFs+ in terms of GM-S at 9M-CA in predicting the presence of RFs+ in the GM-S at 24M-RA were 0.91 (95% CI: 0.59, 1.00) and 0.94 (95% CI: 0.79, 0.99), respectively. This means that the presence of RFs in 9M-CA indicates 91% of children who showed RFs at month 24, and their absence indicated 94% of children who did not show RFs at 24 months of age. A positive predictive value equals 0.83 (95% CI: 0.52, 0.98), which means that the probability of RFs at 24M-RA in children with RFs at 9M-CA is 83%.The negative predictive value is 0.97 (95% CI: 0.83, 1.00), which means that the probability of the absence of RFs at 24M-RA in children without these symptoms at 9M-CA is 97%.

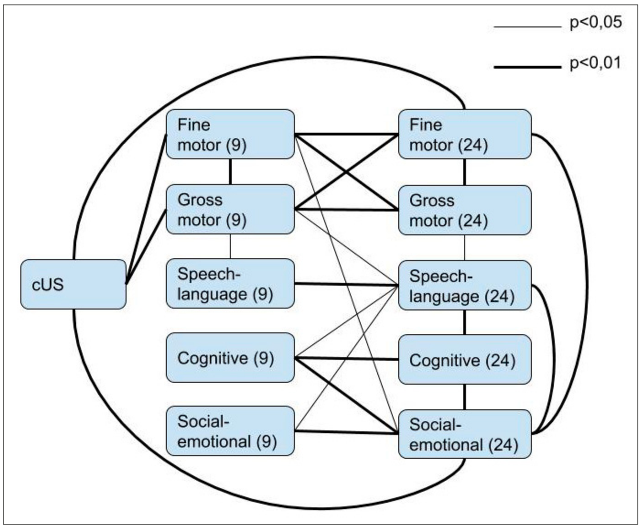

Figure 2. Relationships between the analyzed variables and ultrasound examination of the brain (cUS)

FM-S. The sensitivity and specificity of the presence of alarm symptoms in terms of FM-S at 9M-CA in predicting the presence of alarm symptoms in the fine motor skills at 24 months were 0.83 (95% CI 0.36, 1.00) and 1.00 (95% CI: 0.48, 1.00), respectively. The positive predictive value was 1.00 (95% CI: 0.48, 1.00), and the negative predictive value – 0.97 (95% CI: 0.86, 1.00).

COM. The sensitivity and specificity of the presence of RFs in terms of COM at 9M-CA in predicting the presence of RFs in terms of COM at 24M-RA were 0.27 (95% CI: 0.06, 0.61) and 0.94 (95% CI: 0.79, 0.99), respectively. The positive predictive value was 0.94 (95% CI: 0.79, 0.99), and the negative predictive value – 0.78 (95% CI: 0.62, 0.90).

COG. Sensitivity and specificity of the presence of RFs in the COG at 9M-CA in predicting the presence of RFs in the COG at 24M-RA were 1.00 (0.40, 1.00) and 0.97 (0.86, 1.00), respectively. The positive predictive value was 0.80 (0.28, 0.99), and the negative predictive value – 1.00 (0.91, 1.00).

SO-EM. Sensitivity and specificity of the presence of RFs in the scope of SO-EM in the 9M-CA in predicting the presence of RFs in terms of SO-EM at 24M-RA were 0.43 (0.10, 0.82) and 1.00 (0.90, 1.00), respectively. The positive predictive value was 1.00 (0.29, 1.00), and the negative predictive value – 0.90 (0.76, 0.97).

DISCUSSION

This study concerned assessment of the clinical usefulness of alarm symptoms (so-called 'red flags') of psychomotor development, which were used to predict the development of extreme premature babies. The studied children, born before the end of the 32nd week of pregnancy, are 'at-risk group' for severe neurological sequelae, especially CP and ASD. The seriousness of the problems is proved by unfavourable statistics for these diseases.

CP is the most common childhood physical disability, present in 0.21% of the general population in high-income countries [4]. The frequency of CP presented by Himpens et al. in a meta-analysis of 19 studies in a group of premature babies born before 27 weeks, was 14.6%, whereas in children born between 28 – 31 weeks – 6.8% [13]. Jarjour describes CP being present in 9–20% of premature babies [22]. The results of research carried out by the authors on premature babies showed similar results – cerebral palsy occurred in 9.52%.

Autism spectrum disorder is another serious neurological condition which premature babies are at risk of contracting [23, 24]. ASD is observed in 8% of the extreme premature babies, compared to 0.6% of the population of term-born children [15, 25, 26]. Since the authors examined 2-year-old children, it should be emphasized that the symptoms of ASD before 2 years of age defined the risk of developing disorders in the direction of ASD, while the actual diagnosis is usually made at the age of 3–4 years. It is important to detect the first symptoms as early as possible, therefore screening tests for children aged 18–24 months are recommended. One such test is the M-CHAT questionnaire used by the authors, and its usefulness has been confirmed by many authors [27, 28]. Parents of all children who had alarm symptoms in the final study, were asked to complete the M-CHAT questionnaire. In relation to the entire group of premature babies examined, in 9.52% (n=4 children), the obtained result indicated the

Table 3. Relation between the presence of RFs'+'and RFs'-'at 9M-CA and 24M-RA in the sectors: GM-S, FM-S, COM, COG, SO-EM. RFs '+' – the child did not perform the described skills at 9 or 24 months in developmental sectors; RFs'-'– the child had the correct skills described for 9 or 24 months in developmental sectors.

		GM-S **24M**		FM-S **24M**		COM **24M**		COG **24M**		SO-EM **24M**	
		RFs +	RFs -	RFs +	RFs -	RFs +	RFs -	RFs +	RFs -	RFs +	RFs -
9M RFs +	n	10	2	5	0	3	2	4	1	3	0
	%	83.33	16.67	100.00	0.00	60.00	40.00	80.00	20.00	100.00	0.00
9M RFs -	n	1	29	1	36	8	29	0	37	4	35
	%	3.33	96.97	2.70	97.30	21.62	78.38	0.00	100.00	10.26	89.74
Sensitivity (95% CI)		0.91 (0.59, 1.00)		0.83 (0.36, 1.00		0.27 (0.06, 0.61)		1.00 (0.40, 1.00)		0.43 (0.10, 0.82)	
Specificity (95% CI)		0.94 (0.79, 0.99)		1.00 (0.48, 1.00)		0.94 (0.79, 0.99)		0.97 (0.86, 1.00)		1.00 (0.90, 1.00)	
Positive predictive ratio (95% CI)		0.83 (0.52, 0.98)		1.00 (0.48, 1.00)		0.94 (0.79, 0.99)		0.80 (0.28, 0.99)		1.00 (0.29, 1.00)	
Negative predictive ratio (95% CI)		0.97 (0.83, 1.00)		0.97 (0.86, 1.00)		0.78 (0.62, 0.90)		1.00 (0.91, 1.00)		0.90 (0.76, 0.97)	

necessity to repeat the test and observation in the risk of developing ASD.

In both CP and ASD, early diagnosis is very important for starting therapy. Many studies described relate to separately analyzed symptoms of CP and ASD. Premature babies are at risk for both diseases [23, 29, 30]. Christensen D et al., on the basis of research on a group of 452 children with cerebral palsy, reported that the occurrence of ASD was 6.9% [16]. Other authors give similar observations in the range of 5 – 15% of the examined group of CP children [31, 32]. Symptoms of CP can be diagnosed earlier than the signs of developing ASD. Currently, neurologists report that it is possible to diagnose CP or high risk of CP in infants as early as 6 months of age, based on neurological examination (Hummerschmidt and Neurological Examination – HINE), and assessment of global movements (General Movement Assessment – GMA) in combination with interpretation of MRI head scans [4, 17, 33, 34]. The prognostic value of the HINE study, GMA and MRI of the brain has been scientifically proven [35, 36, 37, 38, 39, 40]. Expert consensus from the American Academy of Pediatrics recommends that a general screener should be used, both when concerns arise during surveillance and routinely at the 9-, 18-, and 24- or 30-month visit, based on the likelihood of disorders being identified by 9- (motor), 18- (communication) and 24- or 30 months (cognitive) [41]. Thus, the use of evidence-based milestones helps detect the early symptoms of the risk of CP, ASD, and other disorders [42, 43, 44, 45]. The authors of the current study compared the predictive value of alarm symptoms appearing in the 9th month in respect of the 24th month, and confirmed their clinical significance in evaluating and forecasting the development of preterm baby. A predictive value for GM-S, FM-S and SO-EM was also observed when abnormal results of ultrasound examination at birth occurred, which has also been observed by other researchers [46].

Preterm delivery changes the developmental trajectories of infants, which may hinder early diagnosis of CP, ASD, or other developmental disorders [47]. According to the authors' experiences, it seems that the 'red flags' chart may improve the CP and ASD risk detection rate in premature babies. Separate analysis of individual developmental spheres or a premature referral to one type of therapy may be the reason for overlooking disorders from another developmental sphere. Qualification to early intervention must be justified and result from strict criteria. Unnecessary therapy can be detrimental to the child and his family, mainly by increasing the level of parental stress [48, 49, 50].

Assessment of psychomotor development using milestones is used primarily for screening, and according to some authors it has important prognostic value [8, 51]. The authors in the conducted preliminary studies observed that RFs of evidence-based milestones serve as a valuable tool for monitoring the development of babies at high risk of developmental disorders, including extreme prematurity. They showed their high practical value, availability and ease of use. Many of the diagnostic methods mentioned above, e.g. the Global Movement Assessment (GMA) and the Test of Motor Performance Measure (TIMP), have a high predictive value, but are limited by the need to complete costly courses [33, 34, 52]. In addition, both methods are used to evaluate only motor development. To evaluate all developmental spheres, the other tests are necessary, and other specialists, e.g. psychologists, speech therapists are needed to assess communication, cognitive and socio-emotional functions. Meanwhile, the application of the described method of monitoring psychomotor development allows family physicians, paediatricians, neurologists and rehabilitation physicians to assess all developmental sectors at the same time. The authors of the current study also used RFs as helpful eligibility criteria for physiotherapy, psychological or speech therapy. The latter application requires testing to confirm observation.

The presented study is a preliminary report which has a main limitation: the small group of examined children. However, the authors point out that the total research period was 3 years: for 12 months, children at risk of abnormal psychomotor development were qualified for the study and their development was monitored for 2 years. Before starting the research, the authors applied practically the development monitoring scheme described in the study. Out of 196 children suspected of developing disorders of psychomotor development, extreme premature babies were selected, who were at the highest risk of neurodevelopmental disorders (NDI). This was an important factor limiting the number of cases studied. Additionally, some children from the selected group did not have complete documentation; therefore the authors did not include them in the statistical analysis. Aware of these limitations, the authors decided to present a preliminary report due to the practical value of the method of monitoring psychomotor development and prognostic possibilities.

The authors are continuing the research, and soon a report on the 3-year period of collecting the studied children and their 2-year follow-up will be presented.

CONCLUSIONS

1. Alarm symptoms (RFs) of milestones are a simple and valuable tool for assessing the psychomotor development of premature babies.
2. The high predictive value of RFs in 9^{th} months in relation to the 24^{th} month allows the use of this tool to assess the development of premature babies.
3. The application of RFs-based developmental monitoring allows for early detection risk of CP, ASD, and other disorders in the group of premature babies.

The study was conducted with the consent of the Bioethical Commission of the Medical University in Lublin (No. KE-0254/222/2017), and is the first part of the research project – a retrospective analysis of the psychomotor development of children at risk. The researchers did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors declare no conflict of interest.

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