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Association Between Neurological Signs and Developmental Outcome: Pilot Results in Preterm Group

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Aim To study the correlations between neurological signs and developmental performance, and to analyze the value of neurological signs in identification of developmental disabilities.

Methods A group of 26 preterm infants (gestational age from 23 weeks to 36 weeks) was studied. The neurological assessment described by Amiel-Tison and Gosselin was performed at term age and repeated every 3 months up to the age of 2, when the sum of all adverse findings was categorized. According to the nature and associations of neurological and cranial signs, patients were divided into 5 categories: 1) cerebral palsy; 2) minimal cerebral palsy; 3) Amiel-Tison triad; 4) intermediate; and 5) normal. Developmental assessment using the Bayley Scales of Infant Development, second edition, was performed between the age of 2 and 3, and the Mental and Psychomotor Developmental Index was determined.

Results The developmental performance was highest in the group of children without neurological signs and lowest in the group with cerebral palsy. There was a strong correlation between neurological signs and mental developmental performance (Spearman $\rho = 0.71$), while the correlation between neurological signs and psychomotor developmental performance was weaker (Spearman $\rho = 0.54$).

Conclusion Categorization of neurological assessment and identification of 3 minor neurological signs may be a valuable tool for early detection of children with developmental disabilities.

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Early identification of children who may show problems in later development is one of the goals of the follow-up of high-risk children. While there is a consensus on the clinical definition of cerebral palsy (CP), milder signs that belong to the same pathophysiology have not been widely recognized (1-3). They are usually called "soft signs" and, being non-specific, are often difficult to elicit or interpret (3,4).

Amiel-Tison et al studied 3 minor neurological and cranial signs, 2 of which refer to passive tone (imbalance in axial tone with excessive dorsal extension, a phasic stretch reflex in one or both gastrocnemius muscles), and a palpable ridge on the squamous sutures. They demonstrated that these signs were important in documenting the relation between mild brain damage and possible future learning disabilities. First, they demonstrated the association between these signs and neuropsychological outcome at 4 years and later they confirmed significant differences according to the presence of minor neurological signs in 3 specific domains of development tested by the Griffiths Mental Developmental Scales: coordination, language, and practical reasoning (3,5).

In order to further analyze the value of neurological signs, as defined by Amiel-Tison et al, to identify developmental disabilities, the aim of this study was to establish the association between neurological and cranial signs detected within the first 2 years and developmental performance (6) of infants between 2 and 3 years of corrected age tested by the Bayley scales.

PATIENTS AND METHODS

Patients

Twenty-six preterm infants (15 female and 11 male) who were at term age between May 2002 and May 2004 referred to the Developmental Department of the Health Center Domžale and whose parents agreed for them to participate were consecutively enrolled in the study. Mean gestational age ± standard deviation was 30.2 ± 3.9 weeks (range 23 to 36 weeks) and mean birth weight was 1607.5 ± 754.8 g (range 525 to 3240 g); 4 children were small and the others were appropriate for gestational age (7). There were 4 sets of twins. They all had one or more neonatal complications. The characteristics of the participants are presented in Table 1 and the characteristics of the normative sample are thoroughly described in the Manual for Bayley scales (6).

TABLE 1. Patient characteristics

Characteristics	Number of infants
Male/female	11/15
Gestational age (weeks):	
23-27	7
28-32	10
33-36	9
Birth weight (g):	
≤999	6
1000-1499	8
≥1500	12
Apgar score <7 at 5 min	7
Mechanical ventilation >1 week	14
Documented sepsis or central nervous system infection	5
Convulsions	2
Hyperbilirubinemia with exchange transfusion	2
Pathological ultrasound:	
intraventricular hemorrhage grade III	2
intraventricular hemorrhage grade IV	1
ventriculomegaly	4
Neonatal neurological assessment:*	
optimal	7
mild/moderate neurological signs	17
severe neurological signs	2

*Amiel-Tison neurological assessment at term age (8).

Neurological examination

Neurological assessment, as described by Amiel-Tison and Gosselin, was performed at term age and repeated every 3 months up to the age of 2 (8-10). It consisted of examination of growth parameters, deep tendon reflexes, cranial suture status, primary reflexes, postural reactions, and evaluation of passive muscle tone. Interpretation of findings relied on the pattern of maturation of 2 motor control systems: the subcorticospinal and corticospinal. Damage to the cerebral hemispheres changes the response to rapid stretching of the gastrocnemius muscles with 2 degrees of severity – a phasic or tonic response. The imbalance in passive muscle tone in the trunk is observed when comparing ventral flexion with dorsal extension (more extension than flexion is abnormal). Damage to the cerebral hemispheres also interferes with head growth and cranial suture status and a ridge on the squamous suture may be palpated in the region of the parieto-temporal suture (11). The signs appear within the first 6-18 months; while the squamous ridge may regress with remolding after 2 years of age, the other 2 signs persist.

The examination was performed by an independent examiner familiar with this method of evaluation. The age of independent walking (corrected for prematurity) was determined by asking the mother at what age the child first walked a few steps without support.

According to the nature and associations of neurological and cranial signs up to the age of 2, when the sum of all adverse findings was categorized, patients were divided into 5 categories: 1) cerebral palsy (1,12); 2) minimal cerebral palsy (uni- or bilateral tonic stretch reflex with or without other abnormalities; independent walking before 2 years of corrected age); 3) Amiel-Tison triad (uni- or bilateral phasic stretch reflex, imbalance of passive axial tone with excessive extension, cranial signs, in particular a ridge on the squamous suture); 4) intermediate (1 or 2 of the 3 Amiel-Tison triad signs); 5) normal (no neurological signs or isolated squamous ridges) (9).

Developmental outcome measures

Developmental assessment using the standardized Slovenian version of the Bayley Scales of Infant Development, second edition (6), was performed blindly between the age of 2 and 3 years by an experienced developmental psychologist. Mean age at the time of testing was 28.3 ± 5.6 months. The Mental Developmental Index (MDI) and the Psychomotor Developmental Index (PDI) were used in the analysis. The mental and motor scales assess the child's current level of cognitive, language, personal-social, and fine and gross motor development. Depending on the developmental age of the child, the MDI includes items that assess memory, habituation, vocalizations, sensory/perceptual acuity, discrimination, acquisition of object constancy, learning and problem solving, early number concepts, generalization, classification, and language and social skills, while the PDI assesses the control of gross or fine muscle skills such as the degree of body control, coordination of large muscles, fine manipulation skills, dynamic movement, postural imitation, and stereognosis. The MDI and PDI, with the standardization mean of 100 and standard deviation of 15 points, indicate a significantly delayed performance if the scores are ≤69 (below -2 standard deviations), mildly delayed performance if the scores are between 70 and 84 (below -1standard deviation), performance within normal limits if the scores are between 85 and 114 (±1 standard deviation), and an accelerated performance if the scores are 115 and above. In 1 case, when raw test scores were so low that the standard score could not be determined, index scores of 49 were given.

Informed consent was obtained from the parents and the study was approved by the National Ethics Committee (No. 145/05/01).

Statistical analysis

The mean and the standard deviation of MDI and PDI scores were used in analysis. The measures of skewness and kurtosis were calculated for the distribution of the MDI and the PDI. The ***z***-scores for skewness and kurtosis were -2.23 and 1.40, respectively, for the MDI, and -1.81 and 0.21, respectively, for the PDI. Both measures were below the limit of *z*-score ±2.58, which should be reached to treat the distribution as significantly skewed or kurtic (13). To compare the results of the studied group with the reference population, a one-group *t*-test was used. The effect size was computed using Cohen *d,* where a *d* of 0.2 represents a small, *d* of 0.5 a medium, and *d* of 0.8 a large effect size (13). To assess the relationships between categories of children according to gestational age, birth weight, and neurological signs with developmental outcome (MDI and PDI scores), Spearman rank-order correlation coefficient (ρ) was used. The *P* values <0.05 were considered significant. Statistical analysis was performed using the SPSS for Windows, version 11.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

In the neonatal period, Amiel-Tison method of neurological assessment revealed optimal results in 7 children: in 5 children the results were also normal during the follow up, while in 2 children intermediate neurological signs were found. Two children with severe neurological signs in the neonatal period were recognized to have CP, which was diagnosed also in 1 child with mild/moderate grade of neurological signs (8). Head ultrasound was abnormal in 7 infants; at the age of 2, CP was identified in 3 of them, minimal CP in 1, Amiel-Tison triad in 2, and intermediate signs in 1 child. Abnormal neurological signs were also found in both children with neonatal convulsions and in 4 out of 5 children with documented sepsis or CNS infection in the neonatal period. During the follow-up, microcephaly was identified in 2 children, but none had severe neurosensory impairment – a hearing threshold higher than 40 dB or vision worse than 6/60.

Developmental outcome vs normative sample

Preterm children in the studied group had significantly lower scores on the MDI and PDI in comparison

with the normative sample (100 ± 15). Their mean score on the MDI (92.5 ± 16.3) was more than one half of a standard deviation below the mean score of the normative sample (t = -2.34, P = 0.027), while on the PDI (84.42 ± 15.48) it was more than one standard deviation below the mean score of the normative sample (t = -5.13, P < 0.001). The effect size for the MDI was in the medium range (Cohen d = -0.50), while for the PDI there was a large effect size (Cohen d = -1.04).

Outcome with regard to neurological signs

Regarding the defined categories, CP was identified in 3, minimal cerebral palsy in 1, and the Amiel-Tison triad in 3 children; intermediate groups with 2 or 1 Amiel-Tison triad signs each consisted of 5 children. In 9 children, no abnormalities were found.

All the children with normal neurological outcome and those from the intermediate group with 1 Amiel-Tison triad sign all walked independently before 18 months of corrected age. In the intermediate group with 2 Amiel-Tison triad signs, only 1 child was a late walker (walked by 19 months), while the others walked on time. Among 3 children with the Amiel-Tison triad, 2 were late walkers, but they all walked by the age of 2. The child with minimal cerebral palsy walked on time, while 2 out of 3 children with CP were non-walkers at 2 years and 1 was a late walker (walked by 20 months). According to the gross motor function classification system for cerebral palsy, 2 of the children had level II and 1 had level I limitations in gross motor skills (14).

Developmental performance

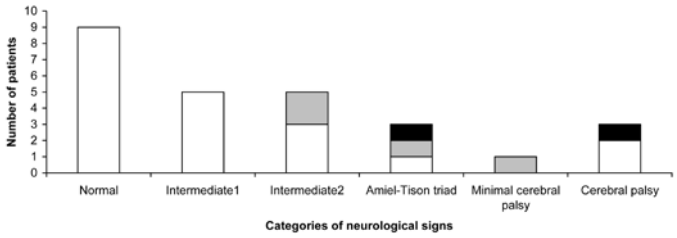
The developmental performance was highest in the group of children without neurological signs, though in a pair of twins with normal neurological outcome mildly delayed performance on PDI was found. Their gestational age was 31 weeks; one of them had sepsis and the other one hyperbilirubinemia. The developmental performance was lowest in the group with CP (Table 2). Mildly delayed performance on the MDI and PDI was more common in the groups with 1 or more neurological signs, while significantly delayed performance on both the mental and motor scales of the developmental assessment was present only in the groups of children with the Amiel-Tison triad and CP. The distribution of MDI and PDI with regard to categories of neurological signs is presented in Figure 1 and 2.

TABLE 2. Mental and Psychomotor Developmental Index according to categories of neurological signs*

Categories	Number of infants	Mean ± standard deviation of MDI	PDI
Normal	9	102.89 ± 8.56	91.89 ± 10.37
Intermediate 1 sign	5	101.40 ± 7.76	90.0 ± 10.27
Intermediate 2 signs	5	89.40 ± 12.09	86.60 ± 12.32
Amiel-Tison triad	3	74.67 ± 17.39	77.00 ± 19.97
Minimal cerebral palsy	1	74.00	73.00
Cerebral palsy	3	75.67 ± 23.29	60.33 ± 17.10
Total	26	92.50 ± 16.33	84.42 ± 15.48

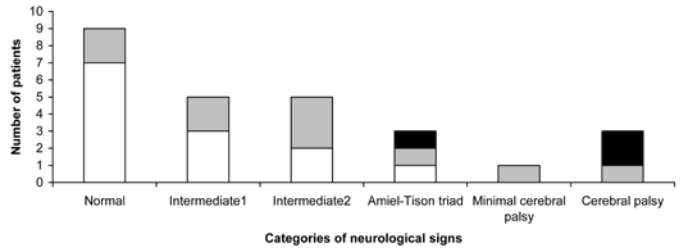
*Abbreviations: MDI – Mental Developmental Index; PDI – Psychomotor Developmental Index.

Figure 1.



Results of Mental Developmental Index regarding the categories of neurological signs. Open bars – within normal limits; gray bars – mildly delayed performance; closed bars – significantly delayed performance.

Figure 2.



Results of Psychomotor Developmental Index regarding the categories of neurological signs. Open bars – within normal limits; gray bars – mildly delayed performance; closed bars – significantly delayed performance.

The correlation between the categories of neurological signs and mental developmental performance was strong (Spearman ρ = 0.71, P < 0.001, n = 26). It was weaker, though still significant, when the children with CP and minimal cerebral palsy were excluded (ρ = 0.60, P = 0.003, n = 22). The correlation between the categories of neurological signs and psychomotor developmental performance was weaker, Spearman ρ being 0.54 (P = 0.004, n = 26) and 0.32

($P=0.141$, n=22), when the children with CP and minimal cerebral palsy were excluded from the analysis.

Developmental outcome regarding gestational age and birth weight

The results on mental and psychomotor domain according to gestational age and birth weight are presented in Table 3. Children with higher gestational age and greater birth weight attained higher scores on both scales. The correlations between categories of gestational age and developmental scores were not significant (MDI: Spearman ρ=0.31, $P=0.127$, n=26; PDI: Spearman ρ=0.28, $P=0.162$, n=26). There was a medium correlation between birth weight and MDI (Spearman ρ=0.45, $P=0.020$, n=26), while the correlation between birth weight and PDI was not significant (Spearman ρ=0.33, $P=0.105$, n=26).

TABLE 3. Mental and Psychomotor Developmental Index according to gestational age and birth weight*

	Number of infants	Mean ± standard deviation	
		MDI	PDI
Gestational age (weeks):			
33-36	9	97.33 ± 10.49	90.22 ± 7.89
28-32	9	97.89 ± 11.26	85.00 ± 17.32
23-27	8	81.00 ± 21.51	77.25 ± 18.42
Birth weight (g):			
≥1500	12	98.92 ± 9.61	89.42 ± 10.98
1000-1499	7	95.29 ± 10.45	85.71 ± 16.67
≤999	7	78.71 ± 22.79	74.57 ± 18.28

*Abbreviations: MDI – Mental Developmental Index; PDI – Psychomotor Developmental Index.

DISCUSSION

The group of 26 preterm infants achieved significantly lower scores on the mental and psychomotor domains of the developmental scales in comparison with the reference population group. Previous studies have demonstrated that the developmental performance in preterm infants and infants with risk factors for developmental delay is significantly lower than in those without risk factors, with the results on the psychomotor developmental scale tending to be lower than on the mental scale when compared with the normative population (6,15). Our results are consistent with these findings and also with the fact that there is a higher incidence of developmental problems in the children with lower gestational age and birth weight (16).

The group of children without neurological signs achieved the highest scores both on the psychomotor and mental developmental scales. A mildly delayed performance was more commonly present in the groups with 1 or more minor neurological signs of the Amiel-Tison triad, while a significantly delayed performance was present only in the groups of children with the Amiel-Tison triad and CP. We found a high correlation between neurological signs and mental developmental performance. Though the correlation was weaker, it was still present when the children with CP and minimal cerebral palsy were excluded from the analysis.

Gosselin et al found a significant correlation between the Amiel-Tison triad and 3 specific domains of mental development: coordination, language, and practical reasoning (3). Contrary to their study in which the Griffiths Mental Developmental Scales were used, we used Bayley scales, which do not differentiate between different domains of mental development. Hence, it was not possible to specify the correlation of minor neurological signs with different domains of mental development. We are also aware of the fact that the Bayley Scales of Infant Development-II have a limited predictive value for a child's later intellectual, language, and achievement performance. The predictive value is higher for lower scores than for scores in the middle and upper ranges if the specific subscales are used and if the child is older than 2 years (6). Minor deficits in particular are often not identified early in life because of the limited sensitiveness of the measures and their inability to detect more subtle problems (15,16). As we intend to follow the children in our study into school age, when more precise neuropsychological instruments are available, we will be able to further analyze the correlations between minor neurological signs and later neuropsychological dysfunction.

Gosselin et al also found that there was less correlation between minor neurological signs and motor domains of development. This was also proven in our study, since we demonstrated that the correlation between the categories of neurological signs and developmental performance was weaker on the motor than on the mental scale (4). This may be due to the fact that the children with neurological abnormalities in the neonatal period were enrolled in the early neurodevelopment intervention program, which stimulates infants' motor development. The other possible explanation for the lower correlation between neurological signs and the PDI is the nature of the testing of motor performance, which only assesses the quantitative rather than the qualitative aspect of motor development (6).

A systematic method for the evaluation of high-risk children should provide a tool for early detection of chil-

dren with past neurological insults and possible future developmental problems to enable the timely enrollment of these children in specific supportive programs. Several approaches have been made to recognize minor neurological dysfunction, as children with minor neurological dysfunction are considered at risk for learning and behavioral problems (4,17-21). The categorization of neurological assessment proposed by Amiel-Tison et al, with the identification of 3 minor neurological signs, enables the understanding of a continuum in the degree of neurological impairments that share the same pathophysiologic background. This was also demonstrated by our finding of a correlation between the progressive decrease in mental and psychomotor performance and the presence of minor neurological signs of the triad.

Despite the fact that our study is pilot and the correlations between neurological signs and developmental performance should be verified on bigger samples of children, we think that our results contribute to the validation of neurological signs as a tool for the detection of children with possible developmental disabilities. We propose to assess them in the process of follow-up of high-risk children.

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