SPECTRUM OF NEURODEVELOPMENTAL DISABILITIES IN A COHORT OF CHILREN IN HUNGARY

Ph.D. Theses

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INTRODUCTION

Neurodevelopmental disabilities are a group of chronic heterogeneous disorders, which include clinically distinct, chronic disorders whose main feature is a disturbance in developmental progress in one or more developmental domains. Neurodevelopmental disabilities have been divided into subtypes, such as global developmental delay, intellectual disability (mental retardation), cerebral palsy, gross motor delay including mostly the neuromuscular disorders, developmental language impairment as a single domain developmental delay and autistic spectrum disorders.

In addition to the main categories of neurodevelopmental disabilities, other subtypes, such as isolated hearing loss, isolated visual impairment, specific learning disability, attention-deficit-hyperactivity disorder, developmental co-ordination disorder ("clumsy" children) etc. also occur, however these conditions and autistic spectrum disorders are not dealt with in this study.

Several population- and cohort-based studies and reviews on the classification and various features of global developmental delay and intellectual disability (mental retardation) have been published earlier, and efforts have been made for the characterization of single domain disorders as well.

Based on the progress in paediatric neurosciences, acknowledging the merits of previous classification schemes, a more refined classification of neurodevelopmental disabilities, including more distinct subtypes of disorders, seems to be required.

AIMS OF THE STUDY

Our aim was to establish a comprehensive classification scheme, rather dissimilar to the previous ones, in order to characterize the spectrum of neurodevelopmental disabilities. An attempt has been made to demonstrate the clinical utility of this classification scheme as an organizing framework for clinical investigations.

The following objectives were targeted by our study:

1. / To perform a retrospective survey of children with neurodevelopmental disabilities in a cohort of patients referred to a paediatric neurology service at a university hospital in South-Eastern Hungary in order

- to estimate the share of neurodevelopmental disabilities among all patients referred to the service

- to establish the spectrum of neurodevelopmental disability subtypes in this cohort of patients
- to search for aetiological factors leading to neurodevelopmental disability
- to estimate the incidence of different severity degrees of intellectual disability (mental retardation) among patients with neurodevelopmental disabilities
- to compare our results with data published by other cohort studies

2. / To establish and manage a regional database for the following purposes:

- to search for environmental factors beyond obstetrical complications responsible for neurodevelopmental disabilities
- to encourage genetic studies to promote preimplantation and prenatal diagnosis in subsequent pregnancies
- to draw the attention of decision-makers to the special needs of children living with neurodevelopmental disabilities

PATIENTS AND METHODS

A retrospective survey of patients with neurodevelopmental disabilities referred to the Pediatric Neurology Service (outpatient and inpatient) at the Department of Pediatrics, Division B, University of Szeged, Hungary between 1 January 2006 and 31 December 2011 was carried out.

The evaluation of patients followed protocols recommended by the Quality Standards Subcommittee of the American Academy of Neurology and The Practice Committee of the Child Neurology Society and other authorities. Special attention has been paid to the presence of malformations and/or dysmorphic features.

Developmental and cognitive evaluations were performed by the Hungarian adaptations of the revised Brunet-Lézine (below 3 years of age), Stanford-Binet (Budapest Binet, between the ages of 3 and 6 years) tests, WISC-IV (Wechsler Intelligence Scale for Children – Fourth Edition, between the ages of 6 and 16 years), and Woodcock Johnson III Tests of Achievement (above 16 years of age). In cases where cognitive functioning was extremely reduced and/or behaviour was substantially disturbed, not allowing the administration of formal test, DQ/IQ scale was assessed indirectly based upon clinical descriptions of the child's functioning.

Developmental delay and intellectual disability (mental retardation) was classified according to the DSM-IV-TR by measure of DQ or IQ as severe/profound (DQ/IQ level below 35-40), moderate (DQ/IQ level 35-40 to 50-55), mild (DQ/IQ level 50-55 to approximately 70), and borderline (DQ/IQ 70-85).

Developmental and neuropsychological assessment was carried out partly by our own clinical testing, partly by personal or telephone interviews. There is a national network of Committees for the Assessment of Learning Abilities and Rehabilitation in Hungary. Infants or children with suspected global developmental delay, or intellectual disability (mental retardation) are entitled to be tested and advised by these committees. DQ/IQ scores were retrieved by personal or telephone interviews from the reports issued by these committees for those patients whose parents were reluctant to expose their children to another test at our department.

Brain imaging (ultrasound, CT, and MRI), EEG, tests for intrauterine infection and screening for inborn errors of metabolism were carried out by conventional protocols. Muscle biopsy specimen was taken from patients with suspected congenital myopathies.

Chromosomal analysis with G-band technique was carried out for patients with dysmorphic features or multiple anomalies. *FMR1* gene test was performed for children with mental retardation if no other etiology was evident. Fluorescence in situ hybridization (FISH) with specific probes or mutation analysis of putative genes was requested for the confirmation of particular diagnoses suspected on the basis of clinical, imaging, laboratory, biochemical, or histopathological features. For a few patients with intellectual disability and dysmorphic features subtelomeric FISH, or array comparative genome hybridization (aCGH) were also carried out.

Patients with traumatic brain injury and CNS infections beyond the neonatal period and children with CNS tumours were not included in this study because special services provide care for these patients in Hungary.

Chi-squared goodness-of-fit test for uniform distribution was used to determine whether any degree of intellectual disability prevailed within a diagnostic subtype, $p \leq 0.05$ was used for establishing statistical significance. Pearson residuals were used as a measure of deviance from the hypothesized uniform distribution.

RESULTS AND DISCUSSION

Total number of 1764 patients was referred to the Pediatric Neurology Service at the Department of Pediatrics, Division B, University of Szeged between 1 January 2006 and 31 December 2011. Neurodevelopmental disability was ascertained in 316 patients (17.9%) and eventually 241 patients (13.7%), who fulfilled the inclusion criteria, were enrolled in this study. The mean age of those who were included was 7.2 ± 4.5 years at the last follow up. There were 131 boys and 110 girls and the male/female ratio was 1.19. The preponderance of males, however, was statistically not significant.

Neurodevelopmental disability occurred **without known prenatal, perinatal, and/or neonatal adverse events** in 167 patients (69.3%), while **known prenatal, perinatal, and/or neonatal adverse events** were responsible for the neurodevelopmental disability in 74 children (30.7%). The subgroups of disabilities and the number of patients in each category are demonstrated in Table 1.

Both static conditions and disorders with a progressive course have been included. We followed the recent concept of Shevell and patients with single domain disabilities, such as isolated motor defect, or developmental (specific) language disorder without intellectual disability were also included in the study. Classification of patients into two major groups based on the absence or presence of definite proof of prenatal, perinatal, and/or neonatal adverse events seems to be justified, because detailed analysis of the prenatal/perinatal/neonatal history can shape the direction of evaluation and has a significant role in determining the aetiology of neurodevelopmental disabilities. Applying this classification scheme aetiology was found in 66.4% of patients. Comparison with other data reported in the literature appears to be difficult as referral pattern, inclusion criteria and methodology are different almost in each study. The aetiological yield figures tended to be about 50-64% in studies, which enrolled patients with global developmental delay without autistic features or children with intellectual disability (mental retardation) only.

Subgroups without known prenatal, perinatal, and/or neonatal adverse events

Genetic syndromes with recognized aetiology comprised 29 patients, 15 boys and 14 girls with mean age of 7.3 ± 4.7 years at the last follow up. Syndromes with numerical/structural chromosomal abnormalities and single gene defects were included in this group. Visual impairment occurred in 2 cases and hearing loss in 2 children. Epilepsy occurred in 6 patients. Moderate intellectual disability was the most frequent (34.5%) among these patients.

A systematic review of the usefulness of various diagnostic investigations in individuals with mental retardation revealed that the frequency of detected chromosomal aberrations was around one in every 10 investigated patients. We found numerical or structural abnormalities (including those ones, recognized only by FISH) in 7.0 per cent of the total patient population in this study. This figure of positive findings however grew up to 12.9 per cent if related to the number of patients in those 4 groups in which chromosomal analysis was mandatory (genetic syndromes with recognized etiology, global developmental delay/intellectual disability (mental retardation) with or without dysmorphic features, and brain malformations).

Clinical symptoms provided the lead to the diagnosis in Prader-Willi, Angelman, Williams, DiGeorge, WAGR and HDR syndromes. A patient with ring chromosome 22 was

Table 1. Classification of 241 patients with neurodevelopmental disability

Subgroups	*No (%)*
Neurodevelopmental disabilities without known prenatal, perinatal, and/or neonatal adverse events	
Global developmental delay/intellectual disability (mental retardation)	
Genetic syndromes with recognized etiology	29 (12.0)
Children with dysmorphic features not recognized as specific syndromes	23 (9.5)
Children without recognized etiology and dysmorphic features	45 (18.7)
Brain malformations	35 (14.5)
Inborn errors of metabolism	6 (2.5)
Leukoencephalopathies	4 (1.7)
Epileptic syndromes	4 (1.7)
Developmental (specific) language impairment	9 (3.7)
Neuromuscular disorders	12 (5.0)
Neurodevelopmental disabilities subsequent to known prenatal, perinatal, and/or neonatal adverse events	
Cerebral palsy after preterm delivery	36 (14.9)
Cerebral palsy after delivery at term	20 (8.3)
Neurodevelopmental disabilities without cerebral palsy	18 (7.5)
Total	241 (100.0)

probably hemizygous for the *SHANK3* gene. In patients with fragile X and Rett syndromes, tuberous sclerosis, neurofibromatosis 1, Waardenburg syndrome and myotonic dystrophy the diagnosis was established on clinical grounds and confirmed by molecular testing in fragile X syndrome, one of the Rett cases, Waardenburg syndrome and myotonic dystrophy. A few genes have been implicated in Cornelia de Lange syndrome, VACTERL association and blepharophimosis–mental retardation syndrome; however our cases are still awaiting their molecular diagnoses.

Global developmental delay/intellectual disability (mental retardation) was associated with **dysmorphic features without** being **recognized as specific syndromes** in 23 children, 13 boys and 10 girls. Their mean age was 7.4 ± 4.0 years at the last follow up. Routine chromosomal studies, *FMR1* gene testing and metabolic screening were normal for all cases and cranial MRI did not reveal any abnormalities except one child who had occipital hypomyelination. Subtelomeric FISH in one case and array comparative genome hybridization in 3 children did not detect any abnormalities. Search for the aetiology by mutation analysis was not successful in finding any mutations in 2 cases. A significant majority of patients (65.2%, $p<0.05$) suffered from severe/profound developmental delay/intellectual disability (mental retardation) in this group.

The co-occurrence of mental retardation and minor anomalies has been suggested long time ago. A 2010 consensus statement by the International Standard Cytogenetic Array Consortium indicated that chromosomal microarray should be the first-line diagnostic test for individuals with global developmental delay or intellectual disability (mental retardation), autism spectrum disorders, or multiple congenital anomalies. As a next step in the diagnostic work up whole-exome sequencing should be considered for the array negative cases. According to these guidelines all patients in this group are candidates for chromosomal microarray followed by whole-exome sequencing depending on the results gained by the array.

Global developmental delay/intellectual disability (mental retardation) occurred **without any recognized etiology and dysmorphic features** in 45 patients, 23 boys and 22 girls with a mean age of 7.7 ± 4.2 years at the last follow up. Routine chromosomal studies, *FMR1* gene testing and metabolic screening were normal for all cases and cranial MRI did not reveal any abnormalities. Array comparative genome hybridization was available only for one child and it was normal. Epilepsy was diagnosed in 13 out of these 45 children (28.9%). A significant majority of these patients (46.7%, $p<0.05$) showed severe/profound defects in their cognitive functions.

Patients with non-syndromic forms of intellectual disability belong into this group. Extensive genetic heterogeneity can be experienced in this type of intellectual disability and great number of autosomal and X-linked causative genes has been recognized by various approaches. Application of new technologies, i.e. chromosomal array and whole exome sequencing can make it theoretically

possible to identify causal mutations in most individuals with intellectual impairment regardless of frequency, heterogeneity, and inheritance.

Brain malformations were revealed by MRI in 35 children, 18 boys and 17 girls. Their mean age was 7.2 ± 4.8 years at the last follow up. Anomalies of the corpus callosum and schizencephaly were the most frequent malformations in this series of patients. Chromosomal abnormalities or inborn errors of metabolism were not found by routine testing. Molecular genetic studies identified mutations in the *GLI3, LIS1, DCX, CEP290, EXOSC3* (2 cases) and *CASK* genes, which means that in 20% of brain malformations the molecular background was detected. Cerebral palsy occurred in 10 cases (28.6%), visual impairment in 12 (34.3%), and hearing loss in 6 patients (17.1%). Epileptic seizures appeared in 12 children (34.3%). A significant majority (60.0%, $p<0.05$) of patients with brain malformations had severe/profound global developmental delay/intellectual disability (mental retardation).

According to the literature 16.3-18% of patients with global developmental delay have cerebral dysgenesis. These figures are close to the frequency of brain malformations in 14.5% of children with neurodevelopmental disabilities in this study.

Although brain malformation was regarded as an etiology of neurodevelopmental disability in our study, the malformations themselves are the sequels of genetic defects or environmental factors. Gene defects can be considered as real aetiologies, while the majority of cases with cerebral dysgenesis await recognition of their real causes, genetic, or environmental.

Inborn errors of metabolism were diagnosed in 6 cases, 5 boys and one girl, their mean age was 8.5 ± 7.8 years at the last follow up. Mutations in the *HPRT* gene were identified in three patients with the X-linked Lesch-Nyhan syndrome and mutations in the mitochondrial DNA occurred in another three patients. Two patients in this group had severe/profound intellectual disability; the cognitive defect was moderate in 3 children and mild in one child.

Overall the yield of metabolic studies is low in patients with neurodevelopmental disabilities and they should be targeted at suspected categories of disorders. The motor disorder and family history in Lesch-Nyhan syndrome, and the clinical features/MRI abnormalities in mitochondrial diseases provided the clue to the correct diagnosis in our cases. The frequency of metabolic disorders among children with global developmental delay was 2-4% in the literature, which figures are in a good agreement with the result of 2.5% in this survey.

Leukoencephalopathies were diagnosed in 4 cases, 2 boys and 2 girls. Their mean age was 4.4 ± 4.0 years at the last follow up. Clinical features and abnormal brain MRI were the clues to the diagnosis in Alexander disease, X-linked adrenoleukodystrophy and Krabbe disease. Mutation analysis confirmed the diagnosis in all 3 cases. In spite of an extended molecular genetic search the aetiology remained unknown in a patient. The global developmental delay/intellectual disability was

severe/profound in patients with Alexander disease and X-linked adrenoleukodystrophy, moderate in the infant with Krabbe disease at 6 months of age and mild in the fourth patient, who suffered from leukoencephalopathy of unknown etiology.

Several leukoencephalopathies are the result of inborn error of metabolism, however the major involvement of the white matter justifies classifying these disorders separately in spite of the obvious overlap with the previous group of patients with neurodevelopmental disorders. The occurrence of leukodystrophy in 2% of patients has been reported earlier in a cohort with global developmental delay, which figure is rather close to the figure of 1.6% in this study.

The role of MRI in the diagnosis of neurodevelopmental disabilities is highlighted by our findings. It proved to be essential in the diagnosis of brain malformations and leukoencephalopathies, and guided the investigations in certain types of inborn errors of metabolism.

Epileptic syndromes were responsible for the neurodevelopmental disability in 4 patients, 2 girls and 2 boys with mean age of 4.8 ± 4.5 years at the last follow up. Devastating infantile migrating partial seizures in association with visual, hearing impairment and severe/profound disability occurred in 2 girls and West syndrome started in infancy in 2 boys who were left with mild cognitive disability. The aetiology of these epileptic syndromes was not identified. Causative mutations in several genes have been identified recently in both syndromes; however molecular genetic tests were not available for our patients. Early onset epileptic encephalopathies with unknown etiology as causes of global developmental delay have not been mentioned in earlier cohort studies, hence comparison was not feasible.

Developmental (specific) language impairment was found in 9 boys. Their mean age was 7.7 ± 2.8 years at the last follow up. Four boys had borderline cognitive impairment, while intellectual disability was not revealed by neuropsychological testing in 5 patients. No aetiology was found in any of these patients.

Predominantly a single developmental domain is affected in developmental (specific) language impairment, although longitudinal studies provided evidence that the delay may not be solely restricted to the language over time. Almost half of our patients had borderline intellectual abilities, which data are in agreement with findings in the literature.

Neuromuscular disorders comprised a group of 12 children, 7 boys and 5 girls. The mean age was 9.8 ± 5.8 years at the last follow up. Molecular genetic testing confirmed the diagnosis in 10 cases. There was no intellectual disability in 58.4% ($p<0.05$) of the patients in this group.

Although neuromuscular disorders constitute an important group of neurodevelopmental disabilities, data on the prevalence of these disorders among children with developmental delay were not available for comparison. A review published on the cognition in neuromuscular disorders and our experiences were in good agreement. There was no cognitive impairment in spinal muscular atrophy,

congenital myasthenia, centronuclear myopathy and one of the patients with nemaline myopathy. Mild or moderate intellectual disability was found in another case with nemaline myopathy, Duchenne muscular dystrophy and facioscapulohumeral dystrophy. Correlation between tissue-specific protein expression and cognitive deficits, however, is still elusive in congenital myopathies.

Subgroups with known prenatal, perinatal, and/or neonatal adverse events

Cerebral palsy due to known adverse events and including patients after preterm, or term delivery was the most common form of neurodevelopmental disability in this study, affecting 23.2 % of the patients, altogether. Cerebral palsy occurred in association with brain malformations as well in 4.2 % of the total population of the cohort, since the total rate of cerebral palsy was 27.4%. These figures are in agreement with literature data, which claim that cerebral palsy is the commonest cause of physical disability in childhood.

Cerebral palsy after preterm delivery was diagnosed in 36 children, 20 boys and 16 girls. Their mean age was 5.8 ± 3.7 years at the time of the last follow up. Most of these children (80.6%) were born at or below 32 weeks of gestation. Symmetrical or asymmetrical germinal matrix/intraventricular haemorrhage and/or periventricular white matter injury occurred in 33 (91.7%) neonates in this group. Spastic quadriplegia was observed in 19 patients (52.8%), spastic diplegia in 9 (25%) and spastic hemiplegia in 7 (19.4%) children. Mixed form of cerebral palsy was found in one patient. Visual loss occurred in 7 patients (19.4%), hearing impairment in 4 (11.1%) and epilepsy in 10 (27.8%) children. The global developmental delay/intellectual disability (mental retardation) was severe/profound in a significant majority of these patients (41.7%, $p<0.05$), while 19.4% of them showed normal intellectual abilities.

Cerebral palsy prevalence increases with lower birth weight and higher immaturity. Our study showed that 43.9% of all cerebral palsy cases were born at or below 32 weeks of gestation in contrast to 25% reported by a European study. These figures emphasize that preventive measures are required to reduce the preterm delivery rate and pay more attention to cerebral protection particularly in very low birthweight infants in the region surveyed. Although the majority of preterm infants with cerebral palsy had severe intellectual disability, it is noteworthy that almost one fifth of them showed borderline, and another fifth normal intellect.

Cerebral palsy after delivery at term developed in 20 children, 10 boys and 10 girls. The mean age was 6.4 ± 3.6 years in this group at the last follow up. Intrauterine growth retardation occurred in 3 cases (15.0%). Severe intrapartum asphyxia was responsible for the cerebral injury in 11 patients (55%), neonatal sepsis/meningitis led to brain damage in 3 children (15%), while neonatal stroke was diagnosed in another 3 neonates (15%). Spastic quadriplegia was observed in 10 (50.0%), spastic hemiplegia in 9 (45.0%) patients and extrapyramidal type of cerebral palsy was found in one case. Visual loss occurred in 3 patients (15.0%) hearing impairment in 2 (10.0%) and epilepsy in 4

(20.0%) children. The global developmental delay/intellectual disability (mental retardation) was severe/profound in 40.0% of the patients, while 30.0% of them showed normal intellectual abilities.

The underlying pathology generally seems to be different in patients with cerebral palsy born at term than in children born preterm. Malformations, cortical and deep grey matter lesions and infarct (stroke) are more common in term born cerebral palsy cases. The spectrum of risk factors and pathologies in our patients (intrapartum asphyxia, intrauterine growth retardation and infections) were in agreement with literature data.

Neurodevelopmental disabilities subsequent to known prenatal, perinatal, and/or neonatal adverse events but **without cerebral palsy** comprised 18 patients with various aetiologies and pathologies. Seven boys and 11 girls with a mean age of 8.2 ± 5.3 years were classified into this group. Eight patients were born at or below 36 weeks of gestation. Intrauterine growth retardation occurred in 3 cases (16.67%). Adverse events included preeclampsia, placental insufficiency, alcohol abuse during pregnancy, intrauterine CMV infection, intrapartum asphyxia and neonatal sepsis. Visual impairment occurred in 3 patients (16.7%) hearing loss in 2 (11.1%) and epilepsy in 2 (11.1%) children. The global developmental delay/intellectual disability (mental retardation) was severe/profound in 44.4% of the patients and it was mild also in 44.4%, ($p<0.05$). The classification criteria excluded patients with normal intellectual abilities from this group. The risk factors and pathophysiology of cerebral injury very likely showed the same pattern as in patients with cerebral palsy discussed above.

In summary, the cognitive disability was severe/profound in a significant majority (41.5%, $p<0.05$) of the 241 patients; it was moderate, mild or borderline in 14.5%, 21.2% and 12.0%, respectively. Defect only in the motor or speech development without global developmental delay/intellectual disability (mental retardation) was found in 10.8% of patients, the majority of them occurred in the groups with developmental (specific) language impairment, neuromuscular disorders and cerebral palsy.

Limitations

This was a retrospective study; therefore, some of the limitations of retrospective studies, such as incomplete data assessment, apply. The results of this cohort study may not be generalized to other populations where medical practice, expertise, referral patterns, accessibility to medical care may be different. Although age specific developmental and intelligence tests were performed for large number of children at our Department, the results obtained by the Committees for the Assessment of Learning Abilities and Rehabilitation, responsible for children's evaluation in Hungary, were also used in several cases. There are also limitations as to the intensity of diagnostic workup. For example, only few patients underwent subtelomeric chromosomal rearrangement, or aCGH screening because of

financial limitations. It applies also to gene tests and next generation sequencing. If these methods were employed more commonly during the routine workup, we would anticipate a higher etiologic yield than that obtained.

Conclusions

This study provides data on the distribution of the various diagnostic categories of neurodevelopmental disabilities in a cohort of patients referred to a paediatric neurology service in Hungary. Overall the aetiology of neurodevelopmental disabilities was identified in 66.4% of the 241 children. Well documented genetic diagnosis (chromosomal numerical/structural abnormalities, or single gene defects) was established in 19.5% of the entire study population. This figure grew up to 28.1% if the number of positive test results was related only to the first major group of patients without known prenatal, perinatal, and/or neonatal adverse events. The degree of global developmental delay/intellectual disability (mental retardation) has also been assessed in each group. Recognition of the causes of neurodevelopmental disabilities helps starting adequate treatment, when feasible and establishing a health maintenance plan and rehabilitation. It provides prediction of the outcome, helps in avoiding unnecessary diagnostic tests and contributes to the prevention of recurrence of the disorder.

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PUBLICATIONS RELATED TO THE THESES

1. Gergev G, Máté A., Zimmermann A., Rárosi F, Sztriha L. Spectrum of neurodevelopmental disabilities: a cohort study in Hungary. *J Child Neurol.* 2015;30:344.356.
2. Gajda A, Horváth E, Hortobágyi T, Gergev G, Szabó H, Farkas K, Nagy N, Széll M, Sztriha L. Nemaline myopathy type 2 (NEM2): two novel mutations in the nebulin (*NEB*) gene. *J Child Neurol. 2015;30:627-630.*
3. Horváth E, Horváth Z, Isaszegi D, Gergev G, Nagy N, Szabó J, Sztriha L, Széll M, Endreffy E. Early detection of Angelman syndrome resulting from de novo paternal isodisomic 15q UPD and review of comparable cases. *Mol Cytogenet. 2013 Sep 8;6(1):35. Doi: 10.1186/1755-8166-6-35.*
4. Gajda A, Szabó H, Gergev G, Karcagi V, Szabó N, Endreffy E, Túri S, Sztriha L. Congenital myasthenic syndromes and transient myasthenia gravis. *Clin Neurosci/Ideggyógyászati Szemle.* 2013;66:200-203.
5. Mokánszki A, Körhegyi I, Szabó N, Bereg E, Gergev G, Balogh E, Bessenyei B, Sümegi A, Morris-Rosendahl DJ, Sztriha L, Oláh É. Lissencephaly and band heterotopia: *LIS1, TUBA1A,* and *DCX* mutations in Hungary. *J Child Neurol.* 2012;27:1534-1540.
6. Szabó N, Gergev G, Kóbor J, Bereg E, Túri S, Sztriha L. Corpus callosum anomalies: birth prevalence and clinical spectrum in Hungary. *Pediatr Neurol.* 2011;44:420-426.
7. Szabó N, Gergev G, Kóbor J, Szűcs P, Túri S, Sztriha L. Holoprosencephaly in Hungary: birth prevalence and clinical spectrum. *J Child Neurol.* 2011;26:1029-1032.
8. Szabó N, Gyurgyinka G(ergev), Kóbor J, Bereg E, Túri S, Sztriha L. Epidemiology and clinical spectrum of schizencephaly in South-Eastern Hungary. *J Child Neurol.* 2010;25:1335-1339.