CONGENITAL MALFORMATIONS OF THE CENTRAL NERVOUS SYSTEM: CLINICAL APPROACH

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Abstract

Central nervous system (CNS) malformations represent important factor of morbidity and mortality in children.

The aim of the study was to determine the incidence, type and clinical features of CNS malformations in children who were admitted at the Neonatal and Child Neurology Department, Neonatal Intensive Care Unit and Paediatric Intensive Care Unit of Paediatric Clinic, University of Sarajevo Clinics Centre, from January 1st, 2002 to December 31st, 2006.

There were total of 16520 admissions at the Paediatric Clinic over the studied period. CNS malformations, solitary or multiple, have been diagnosed in 100 patients (0,61%). The total number of various CNS malformations was 127. Lethal outcome was established in 9/100 cases (9%). The most frequent CNS malformations were neural tube defects 49/127 (38,6%). Hydrocephalus was seen in 34/127 (26,8%), microcephaly in 24/127 (18,9%), agenesis of corpus callosum in 10/127 (7,9%), Dandy Walker malformation in 6/127 (4,7%) and other CNS malformations in 4/127 (3,1%). In 20/100 of patients neural tube defect was associated with hydrocephalus (20%). CNS malformations were prenatally diagnosed in 13/100 of patients (13%).

Primary prevention of CNS malformations can be improved in our country by better implementation of preconceptional folic acid therapy for all women of childbearing age. Secondary prevention by prenatal diagnosis requires advanced technical equipment and adequate education of physicians in the field of foetal ultrasonography. In our circumstances, prenatal diagnostics of CNS malformations is still not developed enough.

KEY WORDS: central nervous system malformations, prevention, prenatal diagnosis

Introduction

Central nervous system malformations are an important problem of child neurology. The term malformation means any morphological abnormality of the CNS that dates to the embryonic or foetal period, regardless of the mechanism of its origin. Neural tube defects (NTDs) account for the most congenital anomalies of the central nervous system (CNS) and result from failure of the neural tube to close spontaneously between the 3rd and 4th week of embryonic development. Major neural tube defects include spina bifida occulta, meningocele, myelomeningocele and encephalocele. Spina bifida occulta consists of a midline defect of vertebral bodies without protrusion of the spinal cord or meninges. Most individuals are asymptomatic and lack neurological signs. In some cases patches of hair, lipoma, discoloration of the skin or a dermal sinus in the midline of the lower back suggests a significant malformation of the spinal cord. Meningocele occurs when the meninges herniate through the defect in the posterior vertebral arches. Myelomeningocele represents the most severe form of dysraphism that involves vertebral column and occurs with an incidence of 1/ 4000 live births. Myelomeningocele may be located anywhere along the neuraxis, however, lumbosacral region accounts for at least 75% of the cases. Hydrocephalus develops in at least 80% of patients with myelomeningocele. Ventricular enlargement may be slow growing or may be rapid (1-3). Surgical treatment of myelomeningocele should be done within a day or so. Surgical closure of the spinal lesion in utero has been successful in a few centres. Intrauterine surgery is based on a hypothesis that exposure of the cord to amniotic fluid increases injury (1,2, 4-9). Encephalocele is a form of dysraphism that affects skull, with protrusion of meningeal sac and cerebral cortex, cerebellum or portions of the brainstem. Agenesis of corpus callosum is relatively frequent CNS malformation, with incidence of 1 to 3 cases per 1000 livebirths. Microcephaly may be subdivided into two types: primary (genetic) and secondary (non-genetic) microcephaly. Secondary microcephaly results from a large number of noxious agents that may affect fetus in utero (1). Dandy Walker malformation consists of a cystic expansion of the 4th ventricle in the posterior fossa and midline cerebellar hypoplasia, as a result of developmental failure in the roof of the 4th ventricle during embryogenesis (1,2). Peripheral malformations commonly accompany CNS malformations. Heart malformations are frequently associated and 7% of children with congenital heart disease also have CNS malformations. The incidence of neural tube defects varies in different parts of the world. There has been a decline in the rate of NTDs in the United States, United Kingdom and Sweden (2, 10-11). In Sweden, approximately 97% of pregnant women attend at least one ultrasound screening during their pregnancy. Maternal serum a-fetoprotein (AFP) screening has been used in Sweden sporadically, while elective abortion due to foetus malformations is allowed until 23 gestational weeks. The sensitivity of maternal serum AFT screening was estimated to be 84-92%. Patients with positive serum screening are usually referred to sonography experts and in these cases the accuracy of diagnosis approaches 100% (11).

The aim of the study was to determine the incidence, type and clinical features of CNS malformations in children who were admitted at the Neonatal Department, Child Neurology Department, Neonatal Intensive Care Unit and Paediatric Intensive Care Unit of Paediatric Clinic, University of Sarajevo Clinics Centre, during the period from January 1st, 2002 to December 31st, 2006.

Patients and Methods

The study was retrospective. CNS malformations were evaluated by different neuroimaging modalities: cranial ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI). All relevant patients' data from personal history, family history, clinical examination and neuroimaging findings were collected and stored in digital form (data base).

Results

There were total of 16520 admissions to the Paediatric Clinic during the study period. Of those, 100 (0,61%) were patients with CNS malformations. These data are shown in the Table 1.

	2002		2003		2004		2005		2006		TOTAL	
Number of admitted patients	2,685		2,895		3,129		3,886		3,925		16,520	
Number of patients with CNS malformations	M*	F**	M	F	M	F	M	F	M	F	M	F
	8	18	11	9	9	9	7	12	13	4	48	52
	26		20		18		19		17		100	
	0,97%		0,69%		0,58%		0,49%		0,43%		0,61%	

* M=male **F=female

TABLE 1. Incidence of patients with CNS malformations for the period 2002-2006

CNS malformations (solitary or multiple) were diagnosed in 100 patients.

Mean gestation age was 39 weeks (X bar =39, SD 2,39).

Mean birth weight was 2982,28 grams (X bar =2982,28; SD 708,88 grams, median 3000 grams)

The lethal outcome was established in 9/100 patients (9%).

The relation between patients with CNS malformations and lethal outcome is shown in Table 2. and Figure 1.

	2002	2003	2004	2005	2006	TOTAL
Number of patients with CNS malformations	26	20	18	19	17	100
Number of patients with lethal outcome	1 3,85%	3 15,00%	3 16,67%	1 5,26%	1 5,88%	9 9,00%

TABLE 2. The lethal outcome in patients with CNS malformations

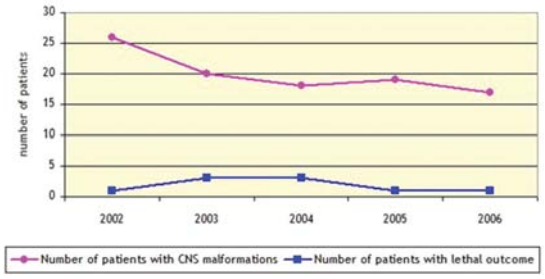

FIGURE 1. The lethal outcome in patients with CNS malformations - graphical view

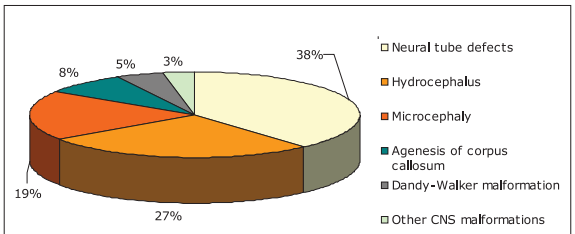

FIGURE 2. The spectrum of CNS malformations

100 patients had the total number of 127 different CNS malformations. The spectrum of CNS malformations was: neural tube defects 49/127 (38,6% of all CNS malformations), hydrocephalus 34/127 (26,8%), microcephaly 24/127 (18,9%), agenesis of corpus callosum 10/127 (7,9%), Dandy Walker malformation 6/127 (4,7%) and other CNS malformations 4/127 (3,1%). The spectrum of different CNS malformations is presented in Figure 2.

The most frequent combination of CNS malformations was neural tube defect and hydrocephalus that was present in 20/100 of patients (20%). CNS malformations have been diagnosed prenatally in 13/100 of patients (13%).

Discussion

The incidence of patients with central nervous system malformations has a trend of slight decline each year, during the study period 2002-2006, while the total number of patients admitted to the Paediatric Clinic has growing trend. But, the total number of 100 patients with CNS malformations (0,61% of total admissions) is important, because of serious medical demands of these patients. Neural tube defects are the most frequent (38,6% of all CNS malformations). Some CNS malformations may be associated with metabolic diseases, like agenesis of corpus callosum. Maternal diabetes mellitus is an important risk factor for the development of CNS malformations. Foetal alcoholism, maternal age over 35 years, multiple pregnancy, oligohydramnion, hydramnion, maternal hyperthermia, use of valproate by epileptic women during pregnancy are important risk factors for the development of CNS malformations. Foetuses that are small for gestation age are also at high risk. The incidence of malformations (any type) in the population of babies who are small for the gestation term is 8%, in comparison to the population of infants of appropriate size for their gestational age where the incidence is 3,3% (3,12). The etiology of CNS malformations remains obscure in most cases. The timing of an insult to the foetus is more important than the nature of the insult in determining the type of resulting malformations. The same noxious agent acting at different periods can produce different malformations. Despite extensive epidemiological studies, the causes of myelomeningocele remain unknown. Causes are likely to be multifactorial, including genetic and environmental factors. Women, who previously have had a child with a neural tube defect, have an approximate 2% risk of recurrence. a-fetoprotein, the principal plasma protein of the foetus, is present in amniotic fluid. Its concentration in the amniotic fluid is increased when plasma proteins exude through a skin defect. Prenatal diagnosis is possible by measuring maternal serum concentration of a-fetoprotein and ultrasound examination of the foetus (2). Prevention is certainly the best form of therapy. Primary prevention of CNS malformations is limited, with an exception of neural tube defects. Periconceptional folic acid supplementation and/or food fortification with folic acid have reduced significantly both the first occurrence and recurrence of NTDs in the offspring (3,11). The consumption of 0,4 mg of folic acid daily is advisable for all women of childbearing age. Women who had delivered an infant with neural tube defects should take

4 mg/day of folic acid from at least 4 weeks before the conception through the first 3 months of pregnancy (2). In some countries fortification of wheat flour is an effective, simple and inexpensive strategy for supplying folic acid, iron and other vitamins to large segments of world population. The world percentage of wheat-flour fortification increased from 18% in 2004 to 27% in 2007 (13-15). In our country, periconceptual folic acid supplementation is not established enough and further efforts should be done to improve it. An early diagnosis of CNS malformations allows a precise prognosis to be made. The efficiency of ultrasound screening in the prenatal diagnosis of NTDs has been demonstrated. The important component of better detection rate of CNS malformations is the improvement in ultrasound technology. The development of techniques for prenatal diagnosis of foetal malformations has raised considerable ethical and practical problems, because of elective terminations (11). Prenatal ultrasound diagnosis of foetal CNS malformations is one possible way of preventing the birth of affected infants. Ultrasonography is used as a routine procedure for the detection of foetal malformations. It is used as basic screening examination for pregnant women due to its efficiency, availability, low cost and real time capability (11). Prenatal diagnostics is not developed in our setting. CNS malformations have been detected prenatally in 13% of patients only. Similar results, from the study of NTD in newborns at Neonatal department of Paediatric Clinic Sarajevo have been published, with detection rate of 14,2%. (12). In Sweden, the prenatal detection rate was 32% (11). Prenatal diagnosis of brain malformations has improved with the advances of imaging techniques (foetal ultrasonography, foetal brain MRI). Prenatal magnetic resonance imaging provides additional information in foetuses with suspected central nervous system malformations. The information obtained from foetal MRI has significant implications for parental counselling regarding both the type of malformation and neurological and developmental prognosis (16-19). Cranial ultrasonography of the newborns with myelomeningocela detects hydrocephalus in 60% of the affected newborns. After the surgical repair of myelomeningocele, hydrocephalus often develops, so hydrocephalus eventually develops in 80 %. The possibilities for active treatment of brain malformations are limited. Hydrocephalus can be effectively managed by ventriculo-peritoneal shunt or other shunting operations. But, even in such cases, neurodevelopmental disorders may persist after successful operation as diffuse brain abnormalities may be present in addition to hydrocephalus. Many of these patients, because of long lasting disorder, need physical therapy and special education (12). In the future, foetal surgical treatment of some CNS malformations should be more frequently applied (5-8). Up to now, no Register for Congenital Malformations has been established in our country, although the first steps were made (20,21).

Conclusion

The possibilities for primary prevention of CNS malformations are limited, but could be improved by better health care for all women of childbearing age and pregnant women. Secondary prevention by prenatal ultrasound screening requires advanced technical equipment and adequate education of the physicians. In our setting, prenatal diagnosis of CNS malformations is not well developed and should be improved.
Foetal MRI should be more frequently used in the evaluation of complex foetal brain malformations. In the future, it is necessary to establish Register of Congenital Malformations in our country.

List of Abbreviations

CNS	-	central nervous system
NTDs	-	neural tube defects
AFP	-	a-fetoprotein
CT	-	computed tomography
MRI	-	magnetic resonance imaging

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