

PHENOTYPICAL PATTERNS IN AGENESIS OF CORPUS CALLOSUM

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SUMMARY: The corpus callosum is a band of white matter, which connects the two hemispheres, its presence being important in coordinating the information and in exchange of sensitive stimuli between the two hemispheres. Early aggression during pregnancy may lead to complete agenesis, while the late once can lead to partial agenesis. IQ of the patients may vary within a large range, being even normal. Agnesis of corpus callosum can be associated with other anomalies of the CNS (Central Nervous System) or chromosomal anomalies. In agnesis of corpus callosum genetic transmission can be either autosomal dominant or recessive X-linked. **Material and methods:** The authors studied a number of 16 patients with partial or complete agnesis of corpus callosum, born between January 2005-January 2009 in Clinical Hospital No.5 "Dr. D. Popescu" by Timisoara, comparing their phenotypes. They were diagnosed antenatal by fetal ultrasound, or postnatal by brain-ultrasound of the newborn, having neurological pathology, during neonatal period, or as a routine examination of a premature baby. **Conclusion:** Comparing the patient's phenotypes, we observed that hypertelorism and broad root of the nose are pathognomonic signs in agnesis of corpus callosum. Outcome of the patients varied, depending on the associated pathology.

Key Words: phenotype, agnesis of corpus callosum, hypertelorism, broad root of the nose.

MODELE FENOTIPICE ALE AGENEZIEI DE CORP CALOS

Rezumat: Corpul calos este o structură de substanță albă care conectează cele două emisfere cerebrale, iar prezența sa este importantă în coordonarea informațiilor și în schimbul de stimuli senzoriali între emisferele cerebrale. Agresiunile timpurii pot conduce la agenezie completă de corp calos, iar cele tardive la agenezie parțială. Coeficientul de inteligență al pacienților variază mult, putând fi și normal. Se poate asocia cu alte anomalii ale SNC, cu anomalii cromozomiale. În agnezia de corp calos transmiterea genetică poate fi autozomal dominantă sau recesivă legată de cromozomul X. **Material și metodă:** Autorii au luat în studiu un lot de 16 pacienți cu agenezie de corp calos parțială sau totală, născuți în perioada ianuarie 2005 - ianuarie 2009 în Spitalul Clinic Nr. 5 "Dr. D. Popescu" Timisoara și au comparat fenotipurile acestora. Diagnosticul a fost stabilit prenatal prin ecografie fetală sau postnatal prin ecografie transfontanelară realizată la nou-născuți cu patologie neurologică în perioada neonatală precoce sau efectuată de rutină la prematuri. **Concluzie:** Comparând fenotipurile pacienților, s-a observat că hipertelorismul și baza nasului lățită reprezintă semne patognomonice pentru agnezia de corp calos. Evoluția cazurilor a fost variabilă în funcție de patologia asociată.

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INTRODUCTION

The corpus callosum is an area of the brain composed of white-matter that connects the two cerebral hemispheres. Its presence is important in coordinating information and for exchanges of sensitive stimuli between the two hemispheres. Until the age of four months of gestation only the rostrum of the corpus

callosum is developed, while the caudal part develops only after the age of five months of gestation. An early aggression during pregnancy leads to complete agnesis, while a late injury leads to a partial absence of the corpus callosum.

The birth defect can be total or partial. In partial agnesis of corpus callosum the posterior area is absent.

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As a consequence of the absence of this part, the two lateral ventricles are separated from the 3rd ventricle, which appears to be superiorly displaced. In some cases appears a nonprogressive, stable dilatation of the caudal part of the lateral ventricles. The IQ varies among agenesis corpus callosum patients, most of them having an IQ situated in the normal range. It is possible that associated abnormalities of the CNS are responsible for mental retardation.

In agenesis of corpus callosum there are known two types of inheritance: autosomal recessive inheritance and X-linked dominant inheritance. Sometimes, this structural anomaly of the CNS is associated with chromosomal aberrations. Most commonly associated syndromes are: trisomy 8, 13 or 18.

MATERIAL AND METHODS

We studied a group of 16 patients, born between January 2005 - January 2009 in Clinical Hospital Nr. 5 "Dr. D. Popescu", Timisoara, diagnosed with complete or partial agenesis of corpus callosum. Among them 9 were females and 7 males. The diagnosis of agenesis of corpus callosum was established either by antenatal ultrasonography, or by postnatal ultrasound examination of the newborn and confirmed by MRI of the brain.

Patients have been included in the study during their neonatal period and followed-up periodically by the Department of Medical Genetics of the UMFT and also by many medical specialists, including an ophthalmologist, pediatric neurologist, ear-nose-throat specialist. For all patients karyotype analysis was performed. The newborns were children of young, healthy parents, except one who's mother was oligophrenic.

Half of the patients resulted from natural birth, while the other half were delivered through caesarean section. 62,5% of the patients (10) were born at term, while 37,5% (6) were preterms, with gestation ages between 28-36 weeks. Birth weight ranged between 800-3700 grams.

RESULTS AND DISCUSSION

The 16 cases were classified as follows:

- isolated agenesis of corpus callosum (2)
- agenesis of corpus callosum combined with other syndromes: trisomy 8 (1), trisomy 13 (1), trisomy 21 (2), trisomy 18 (1), oro-facial-digital syndrome (2), other syndromes.

In two cases the diagnosis of agenesis of corpus callosum was established antenatal by ultrasonography, while in other 6 cases the associated cerebral abnormalities were diagnosed antenatal (hydrocephalus,

porencephalic cyst). The rest of the cases were diagnosed postnatal by continue ultrasound examination of the brain, in term or premature babies, who had neurological signs in early neonatal period. The cases with isolated agenesis of corpus callosum were asymptomatic at birth, both agenesis being partial and were diagnosed by postnatal ultrasound examination, the patient being both premature. Neurological signs occurred in 5 cases (31,25%), as seizures within the first 72 hours of life.

The phenotypic spectrum of the patients is described in table 1, hypertelorism and broad root of the nose occurring in all patients as pathognomonic signs. In phenotype were emphasized other phenotypic characteristic features, too.

The outcome was different: newborn with isolated agenesis of corpus callosum and in those who had associated macrocephalus, neurological development was according to their age. Seizures repeated in all patients with seizures in the early neonatal period. In trisomy 21 syndrome the mental retardation, characteristic for this disease, occurred, while spastic tetraparesis was described in two cases of prematures with extreme low birth weight (800 grams, gestation age=28 weeks), who presented multiple complications of prematurity in early neonatal period: requiring resuscitation and ventilation. Death occurred in 5 of the most severe cases (31,25%). Chronic intrauterine infections of the TORCH syndrome didn't occur in patients with congenital hydrocephalus, cerebral malformations (porencephalic cyst).

CONCLUSIONS

Agenesis of corpus callosum is a cerebral malformation without clinical evident symptomatology, in many cases being diagnosed incidentally. Antenatal diagnosis of agenesis of corpus callosum is difficult to achieve because usually fetal ultrasound emphasizes the associated cerebral anomalies of the fetus.

Once found, the disease makes us think that we are in front of a chronic maternal-fetal infection, a genetic syndrome, a chromosomal disorder or an isolated agenesis of corpus callosum. The phenotype is characteristic for syndromes in which the anomaly occurs, the only common signs being hypertelorism and broad root of the nose.

It is the role of the neonatologist to certify the diagnosis and to guide the case to a genetician, genetic counseling being extremely important to the family. Brain ultrasound is a very important non-invasive investigation

and performing it in the neonatal period should be a emphasizing late symptoms, which will influence the screening in all mate/ rnities. Follow-up is important for newborn’s behavior.

Table 1

Type of agenesis	Number of cases	Diagnosis	Phenotype
Isolated ACC	2	Postnatal brain ultrasound	Hypertelorism Broad root of the nose
ACC + microcephalus	1	Antenatal	Hypertelorism Broad root of the nose Large ears
ACC + macrocephalus	1	Postnatal brain ultrasound	Hypertelorism Broad root of the nose Low set ears Narrow palate
ACC + congenital hydrocephalus	2	Antenatal hydrocephalus	Macrocephalus Hypertelorism Broad root of the nose
ACC + Trisomy 8	1	Antenatal hydrocephalus	Hypertelorism Broad root of the nose Small nose Large mouth Micro-retrognathia Small mandibula Posterior set ears
ACC + Trisomy 13	1	Antenatal hydrocephalus	Hypertelorism Broad root of the nose Proboscis Antimongoloid palpebral fissures Low set ears
ACC + Trisomy 21	2	1 antenatal 1 postnatal brain ultrasound	Hypertelorism Broad root of the nose Mongoloid palpebral fissures Small, low set ears Protrusion of the tongue Sign of the “sandal” Long, thin fingers
ACC + Trisomy 18	1	Postnatal ultrasound	Hypertelorism Broad root of the nose Large, sharp, low set ears Short palpebral fissures Epicanthus Narrow palate Microstomia
ACC + cerebral malformation (porencephalic cyst)	1	Antenatal cerebral malformation (cyst)	Microcephalus Hypertelorism Broad root of the nose
ACC + spastic tetraparesis	2	Postnatal brain ultrasound	Hypertelorism Broad root of the nose Micrognathia Narrow palate
ACC + oro-facial-digital syndrome	2	Postnatal brain ultrasound	Hypertelorism Horizontal palpebral fissures Broad root of the nose Cleft tongue Short philtrum Small mouth Low set ears

Table 2

	Isolated ACC	ACC + microcephalus	ACC + macrocephalus	ACC + congenital hydrocephalus	ACC + Trisomy 8	ACC + Trisomy 13	ACC + Trisomy 21	ACC + Trisomy 18	ACC + Cerebral malformation (porencephalic cyst)	ACC + Spastic tetraparesis	ACC + oro-facial-digital syndrome
Phenotype					Cleft tongue Mongoloid palpebral fissures Single crease at the fifth finger Clinodactyly of the second finger Cleft between the second and third toe Anterior set anus Left choanal atresia			Proeminent occiput Clinodactyly Brachydactyly Arthrogyposis "Piolet" leg			Short limbs Hypoplastic thorax Skull in shape of clover Malformation of the fingers
Symptomatology	Asymptomatic	Seizures	-	-	Seizures	Heart failure	-	-	Seizures	BMH	-
Outcome	According to age	Seizures	According to age	Death	Seizures	Death	Mental retardation	Motor deficit	Seizures	Seizures	Death
Observations		No occurrence of TORCH syndrome								Psychomotor retardation GA = 28 weeks Multiple resuscitation	

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