Retrospective study of the characteristics of craniospinal disorders diagnosed prenatally

Theses of doctoral (PhD) dissertation

Written by Dr József Gábor Joó
Consultant: Dr Zoltán Papp, professor

Doctoral School of Semmelweis University
Clinical Medicine (head: Dr Zsolt Tulassay, professor)
Foetal and Neonatal Medicine (head of programme: Dr Zoltán Papp, professor)

Faculty of General Medicine, Semmelweis University
1st Department of Obstetrics and Gynaecology
Budapest, 2005.
INTRODUCTION

As far as their morphology and aetiology are concerned, craniospinal malformations present a heterogeneous group of congenital disorders. Several pathological factors are known to contribute to their development. Although certain cerebrospinal malformations could be diagnosed in the early periods of the development of ultrasonography, this group of malformations has been in the focus of attention ever since, which can be explained by the high incidence and usually bleak prognosis of these diseases.

GOALS

The Genetic Counselling Unit at our department has been one of the largest genetic centres in Hungary since 1990. In addition to couples referred to our unit in the frame of progressive health care, the number of expectant couples seeking help on their own has been on the rise.

Among others, one of the most important tasks of our centre involves the earliest possible recognition and detection of congenital disorders, including craniospinal malformations.

The goal of my study is to find answers to the following questions:

1. Is there any relationship between parental age and the incidence of the craniospinal disorders in question and, also, if gravidity, i.e. the number of the given pregnancy has any role at all?
2. What is the gender distribution in the various cerebrospinal disorders?
3. How important is the patients’ positive history in the development of disorders?
4. When are the individual types of disorders diagnosed during pregnancy?
5. What are the major associations of certain malformations affecting the central nervous system and what are typical associations other than those of the CNS in the different types of the aforementioned malformations?

6. What is the importance of ultrasonographic diagnostics and maternal serum alpha-foetoprotein levels in the diagnostics of the malformations in question?

7. What is the proportion of chromosomal disorders among the examined cases?

8. How important are intrauterine infections in the etiology of cerebrospinal development disorders?

9. What was the outcome of pregnancies in the cases examined by us, with special regard to cases of corpus callosum dysgenesis?

10. What was the outcome of subsequent pregnancies; what was the special foetal risk in the different types of disorders, and the risk of recurrence, followed up in five-year periods?

**MATERIAL AND METHODS**

In this study, I have processed the data of 1689 craniospinal malformations that were diagnosed at the Department of Obstetrics and Gynaecology, Medical University School of Debrecen and the Genetic Counselling Unit of the 1st Department of Obstetrics and Gynaecology, Faculty of General Medicine of Semmelweis University, in the 25-year-period between 1976 and 2001.

I am going to give a survey of the main characteristics of anencephaly (385 cases), corpus callosum dysgenesis (28 cases), encephalocele (51 cases), holoprosencephaly (50 cases), hydrocephalus/ventriculomegaly (412 cases), hydrancephaly (9 cases), microcephaly (64 cases), spina bifida (307 cases), as well as spina bifida + hydrocephalus (372 cases) from demographic, diagnostic and prognostic points of view alike.
I put great emphasis on mapping the demographic characteristic as well as familiarising with the details of the patients’ genetic, obstetrico-gynaecological and general history.

Ultrasonographic investigations, playing a key-role in making a diagnosis, were done in the ultrasound laboratories of the Department of Obstetrics and Gynaecology of the University Medical School of Debrecen and our department.

The majority of chromosome investigations, performed for various other reasons (e.g. parental age), involved ultrasound-controlled transabdominal genetic amniocentesis (GAC), but, occasionally, chorionic villi sampling (CVS) was also included.

If craniospinal malformations (ventriculomegaly-hydrocephalus) were suggestive of a previous infection, TORCH test (Toxoplasma, Others, Rubeola, Cytomegalovirus, Herpesvirus) was performed.

In cases with corpus callosum dysgenesis – concerning the outcome of pregnancies – the psychomotor development of children was evaluated using the Binet-Simon test and Brunet-Laisine test at the Neonatological Follow-up Unit of our department and the data were included in my investigations.

I used the databank of the Genetic Counselling Unit in statistical data processing. Processing the individual numerical data, I applied statistical calculations such as median, mean value and significance calculations, and SD and sensitivity calculations. (Calculating significance, I used the Chi-square [$\chi^2$] test).

RESULTS
Maternal and paternal age
The incidence of maternal age below 18 hardly exceeded 2.5% among all of the examined disorders, while the share of those over 40 years of age was even
less, below 1%. Two-thirds of all of the cases could be associated with mothers aged between 21 and 30 years.

As far as the fathers’ age was concerned, extreme age groups had a similar proportion to that of the mothers’ in the whole of the sample, the difference being that among the fathers more people were found to be over 40 years of age.

Comparing the different disorders with high incidence I concluded that in cases of spina bifida+hydrocephalus and hydrocephalus alone, the maternal age over 30 was more common than in the other disorders included in this study. Hydrocephalus was found to be more common in the second than in the first pregnancies.

**Gender distribution among the fetuses**

Regarding all of the disorders in the sample, the proportion of boys and girls was 47% and 53%, respectively.

In case a malformation with higher incidence was studied, it could be observed that the number of female foetuses exceeded that of the male ones, the differences being significant.

**History**

In approximately a quarter (25%) of all of the cases there was a positive obstetrical-gynaecological history; a positive genetic history and positive general medical history were found in approximately 9% and 2.5%, respectively.

**Time of making a diagnosis**

I paid distinguished attention to the interval between the 12th and 35th gestational weeks in checking the time when the diagnosis was made.
On analysing the disorders of high incidence it could be seen that anencephaly was typically diagnosed in the 17-20\textsuperscript{th} gestational weeks, i.e. after ultrasonography, performed in the possession of the maternal AFP-findings, while the diagnoses of spina bifida cases were much more evenly distributed between the 18\textsuperscript{th} and 24\textsuperscript{th} gestational weeks.

The individual characteristics of a disorder in question were most expressed through the times of diagnosing the cases of hydrocephalus; the almost even distribution of diagnoses between the 16\textsuperscript{th} and 32\textsuperscript{nd} gestational weeks was in good correlation with the complex aetiology of this malformation as well as its appearance at highly different times during intrauterine development.

**Other developmental disorders of the central nervous system associated with the malformations included in the study**

Among the 385 examined cases of anencephaly, 101 (approx. 26\%) were associated with some other disorders affecting the central nervous system.

By magnitude, encephalocele, spina bifida and holoprosencephaly could be justified in similar proportions. The association of corpus callosum cases with some disorders of the central nervous system in approximately 53\% deserves attention.

**Association of malformations with disorders other than those of the central nervous system**

Among the diseases of the cardiovascular system, ventricular septal defect (VSD) and singular umbilical artery were found in association with almost all of the diseases of the central nervous system included in this study.

Malformations of the gastrointestinal system involved intestinal malrotation, while pyelectasy was often found as one of the commonest genitourinary disorders.
Among the facial disorders, cheilognathopalatoschisis was found to be the most frequently associated malformation affecting other than the central nervous system, while the commonest thoraco-abdominal disorders included associating diaphragmatic hernias and omphalocles.

**Ultrasonographic diagnostic characteristics of certain craniospinal disorders**

In the case of spina bifida, the exact localisation of the lesion is essential as, apart from its importance in prenatal diagnostics, this finding is also of clinical importance. The involvement of the lower vertebral segments was found significantly greater than that of the higher ones.

On investigating the occipitofrontal diameter (OFD), the incidence of values associated with the 50 percentile of the gestational age of the pregnancy in question was lower than 15%, while the proportion of OFD values above 90 percentile was more than 50% compared to all of the diagnosed cases.

**Alpha-fetoprotein levels in maternal serum**

Most of the cases with increased maternal serum alpha-foetoprotein levels were found in anencephaly, as the proportion of values exceeding 2.5 MoM was more than two thirds of all of the disorders included in the study. In addition to anencephaly, the dominance of elevated serum AFP levels could be detected in two other “open” lesions such as spina bifida and spina bifida associated with hydrocephalus (SB+HC) (53% and 59%, respectively).

On investigating corpus callosum dysgenesis, encephalocele and microencephaly, the majority of the AFP levels were found in the normal physiological range.

As far as the efficiency of the method and other comparisons with the other six disorders included in the study were concerned, serum AFP
investigations in anencephaly, spina bifida and spina bifida+hydrocephalus showed significant differences (p<0.02).

**Intrauterine karyotyping**

Intrauterine karyotyping was performed in approximately a quarter of all of the cases (434 cases). The investigations were indicated due to a higher risk of chromosomal disorders suspected because of other reasons.

Pathological karyotypes were justified in anencephaly and holoprosencephaly in two cases each, and hydrocephalus and SB+HC, one case each.

Of the six abnormal findings three involved 21-trisomy, one was characterized by 18-trisomy and two of them turned out to be mosaic conditions.

**Outcome of the pregnancies**

In the majority (98%) of cases with neural tube closure defects the pregnancies were terminated.

Induced abortions were performed in six of the twenty-eight pregnancies with corpus callosum dysgenesis; there were no data available about three further cases. Among the remaining 19 cases, the intelligence tests conducted at the Neonatology Follow-up Unit at our department showed normal mental development in eight children; in five cases mental retardation was found while the rest justified cerebral atrophy, periventricular leucomalacia and holoprosencephaly.

**Share of the above disorders in multiple pregnancies**
Of the 1678 investigations, twenty-one (1.25%) were detected in multiple pregnancies. In the majority of these pregnancies one of the foetuses was found healthy but in eight cases craniospinal malformation was seen in both foetuses.

The pregnancies were terminated due to anencephaly despite the fact that, together with the anencephalous one, a healthy twin foetus had been detected in the ultrasonographic investigations in three of the cases.

Multiple pregnancies with spina bifida are worth special mentioning because induced abortions, induced premature deliveries and normal deliveries were also found as the outcome of pregnancy among them.

A similarly “colourful picture” was seen concerning the outcome of multiple pregnancies with hydrocephalus, a selective induced abortion performed in the 22nd gestational week being included among the cases.

**Outcome of subsequent pregnancies in patients included in the study**

Subsequent pregnancies after anencephalies resulted in healthy mature live newborns in approximately 85% of the cases. In approximately 6%, however, early or second-trimester obstetric complications (miscarriage, missed abortion) developed and in more than 9% of all of the cases genetic disorders were diagnosed.

Among the eight subsequent pregnancies following corpus callosum dysgenesis, three (37.5%) were associated with obstetric complications, but no genetic disorders were described in them.

In subsequent pregnancies with encephalocele in the past history, the proportion of healthy live mature babies (82%) was similar to the one in cases of anencephaly.

It should be mentioned, however, that in subsequent pregnancies after holoprosencephaly the incidence of early and second-trimester obstetric complications (miscarriage, missed abortion, intrauterine death) was quite high, over 21%.
Risk of repetition in the individual disorders

Basically, the risk of repetition was in correlation with the values known from multifactorial aetiology; our values concerning the risk of repetition were in the range of 3 – 6%. Examining five-year-periods in the cases of neural tube closure defects and combined spina bifida-hydrocephalus malformations, we found a decrease in the risk of repetition, while in the case of hydrocephalus, the risk of repetition was more or less constant.

CONCLUSIONS

1. Based on the 1678 cases in this study, there was no direct correlation between maternal age and the incidence of craniospinal malformations in question. It should be noted, however, that hydrocephalus alone and in combination with spina bifida occurred more frequently if maternal age was over 30.

   Anencephaly and hydrocephalus were more often found in the second pregnancy, moreover, hydrocephalus occurred more frequently in the third, fourth and umpteenth pregnancy than any of the other disorders.

2. It could be concluded that the disorders in question – as a whole – occurred a bit more frequently among girls than boys. This conclusion is most marked in anencephaly, although it also applies in the two other forms of neural tube closure defects.

3. On dividing positive histories into three groups, positive genetic, obstetric and general histories were found in 8.7%, 24% and approximately 2.5%, respectively.

   Based on the above, in genetic counselling, special emphasis must be given to familiarising with the gravida’s detailed obstetric history – in addition to taking the patient’s genetic history in detail. Moreover, it should also be considered that, together with the traditional indications by a genetic
counsellor (positive genetic history, age, ultrasonographic changes), a positive obstetric history should also be included among the indications for counselling in pregnancy.

4. On the basis of the investigations it can be claimed that up-to-date ultrasonography and maternal serum alpha-foetoprotein findings (if necessary, amniotic fluid AFP findings) give an opportunity to safely diagnose the disorders in question.

In pregnancies in which the incidence of cerebroventricular dilation exceeds that of the level of the general population, prenatal genetic follow-up is recommended for a long time, possibly till the end of the pregnancy.

5. It should be considered in daily genetic counselling that in cases in which cerebroventricular dilation is diagnosed, special attention is to be paid to its possible association with corpus callosum dysgenesis as this question is of utmost importance in the prognosis of the pregnancy, deciding about further prenatal care and setting the time of the termination of the pregnancy. Anyway, the assessment of other disorders of the central nervous system associated with corpus callosum dysgenesis is a major point in making the final decision about the fate of the pregnancy.

The assessment of associated disorders other than those of the central nervous system are of special importance in craniospinal malformations in which nervous system disorders are not incompatible with life. So a decision about the fate of the pregnancy or further prenatal care is greatly dependent on the presence of other organic disorders.

6. Examining the localisation of spina bifida, I found that the lesion was situated in the lumbar region or caudad to this region in approximately 75% of the cases.

Concerning practical ultrasonographic diagnostics, more emphasis should be given to OFD values in the ultrasonography of hydrocephalus and the evaluation of the findings.
The highest sensitivity of maternal serum AFP values was seen in neural tube closure defects.

7. It could be concluded that the association of the investigated craniospinal disorders and chromosome aberrations was insignificant.

Based on the data of my investigations, in the cases in which counselling was offered due to an increased risk of craniospinal malformations, there was no need to perform intrauterine karyotyping, holoprosencephalies suggested by ultrasonographic findings being the only exceptions.

8. On the basis of the results it can be confirmed that it has been an established practice in genetic counselling to recommend the performance of a TORCH serological investigation of the gravida if the value(s) of the lateral ventricles exceed the physiological level, or if the biometric findings are suggestive of microcephaly. In certain cases, to confirm a suspected Toxoplasma infection, amniocentesis for sampling the amniotic fluid for Toxoplasma-DNA investigations can also be considered.

9. In everyday genetic counselling, cases with hydrocephalus must be thoroughly examined to exclude a possible intrauterine infection or other disorders, which are likely to associate with hydrocephalus. These cases should be controlled on a regular basis as professional genetic care or programmed delivery may give a good postnatal prognosis for the foetus, in addition to neurosurgical care, which is available if necessary.

In the case of corpus callosum dysgenesis, the associated disorders of the central nervous system (which are relatively frequent) should be excluded as early as possible as, in the case of isolated disorders, the postnatal prognosis is regarded to be good in a great share of pregnancies. It must be mentioned, however, that among children suffering from this disorder neurological complications are significantly more frequent, therefore postnatal follow-up is also of great importance.
In multiple pregnancies discordant to cerebrospinal malformation, a decision about the fate of the pregnancy has to be based on the complex analysis of several standpoints as, among others, the severity of the disorder, gestational age, and the involvement of foetus A or B are important factors, which may basically influence the decision.

Explicit decrease has been found in the values of risk of repetition in neural tube closure defects, while a similar decline has not been seen in holoprosencephaly, hydrancephaly or hydrocephalus. Based on the above, the importance of consequent periconceptional and prenatal folic acid supplementation must be emphasized as it plays an important role in the decrease of the risk and primary prevention of the repetition of neural tube closure defects.
   Prenatal diagnosis, phenotypic and obstetric characteristics of holoprosencephaly  
   Fetal Diagn. Ther. 20, 161-166

   Trisomy 20 mosaicism and non-mosaic trisomy 20  
   J. Reprod. Medicine (megjelenés alatt)

   A holoprosencephalia szülészeti, praenatalis diagnosztikai és phenotypusos jellemzői  
   Magy. Nőorv. L. 67, 3-10

   Successful pregnancy in a Noonan-syndrome patient after 3 unsuccessful pregnancies from severe fetal hydrops  
   J. Reprod. Medicine 50, 373-376

   A ventriculomegalia/hydrocephalus kóreredete 230 prenatalisan diagnosztizált eset kapcsán I.  

   A ventriculomegalia/hydrocephalus praenatalis diagnosztikája 230 vizsgált eset kapcsán II.  

   Trisomies and other chromosome abnormalities detected following positive sonographic findings  
   J. Reprod. Medicine 50, 675-691
8. Papp Cs., Tóth-Pál E., Beke A., Bán Z., Joó JG., Szigeti Zs., Csaba Á.,
   Chorionboholy-mintavétel és amniocentesis: az invazív beavatkozások és
   kockázatuk napjaink prænatalis diagnosztikai gyakorlatában
   Orv. Hetil. 145, 315-321

   Noonan-szindrómás beteg sikeres terhessége három, súlyos magzati
   hydropsszal járó sikertelen terhességet követően

    Cs., Papp Z. (2005)
    Toxoplasma gondii kimutatása magzatvízből fluorescens-PCR és DNS
    fragmentanalízissel
    Magy. Nőorv. L. 68, 95-100

    Postnatalis vizsgálattal igazolt VACTERL-Hydrocephalus-szindróma esete
    Gyermekgyógyászat 55, 59-63

12. Szigeti Zs., Tóth-Pál E., Papp Cs., Beke A., Joó JG., Bán Z., Mezei G.,
    Cytogenetic investigation of fetuses conceived by intracytoplasmatic
    sperm injection
    Prenat. Diagn. 24, 579-580

    Cs., Papp Z.
    A 20-as chromosomát érintő numerikus illetve strukturális eltérések
    Magyar Nőorv. Lap. (megjelenés alatt)

    Ultrahangvizsgálatt al észlelt magzati anomáliák cytogenetikai exploratíója
    Orv. Hetil. 145, 2123-2133

BOOKS


A cervixalis intraepithelialis (CIN) terhesség alatti diagnosztikája és terápiája

**OTHER BOOKS**

1. **Joó JG.** (2005)
Terhesgondozás ikerterhességben
In: A várandós nő gondozása. Szerk.: Rigó J. jr., Papp Z.
Medicina Könyvkiadó, Budapest, pp. 281-290

2. Silhavy M., **Joó JG.** (1999)
A méhtevékenységet befolyásoló gyógyszerek
In: Gyógyszeres therapia a szülészet-nőgyógyászatban. Szerk.: Papp Z.
MediMedia Kiadó, Budapest, pp. 41-46

Terhesség alatti gyógyszeres kezelés
In: Gyógyszeres terapia a szülészet-nőgyógyászatban. Szerk.: Papp Z.
MediMedia Kiadó, Budapest, pp. 29-41

Fogamzásgátlás
In: Gyógyszeres terapia a szülészet-nőgyógyászatban. Szerk.: Papp Z.
MediMedia Kiadó, Budapest, pp. 25-29

**ABSTRACTS**

1. Beke A., Papp Cs., Tóth-Pál E., Mezei G., Oroszné N.J., **Joó JG.**, Csaba Á., Papp Z.
Chromosome abnormalities detected following positive ultrasound finding
XVIII International Congress "The Fetus as a Patient", Budapest, 2002
Fetal Diagn. Ther. 17 (Supplement 1), 47


5. Beke Anna, **Joó JG.**, Papp Z. (2005) Follow-up studies of newborn babies with corpus callosum dysgenesis 5th Graz Symposium on Developmental Neurology


19
   A holoprosencephalia szülészeti, prænatalis diagnosztikai és phenotypusos jellemzői Magyar Humánogenetikusok V. Munkakonferenciája, Szeged, 2004

    Chromosoma-rendellenességek előfordulása egyoldali és kétoldali plexus chorioideus cysta esetén
    Magyar Humánogenetikusok V. Munkakonferenciája, Szeged, 2004

    Prenatal diagnosis, phenotypic and obstetric characteristics of holoprosencephaly
    7th World Congress of Perinatal Medicine, Zágráb, 2005
    J. Perinat. Medicine 33 (Supplement 1), 163

    7th World Congress of Perinatal Medicine, Zágráb, 2005
    The risk of aneuploidies in cases of choroid plexus cysts
    J. Perinat. Medicine 33 (Supplement 1), 162

    12th International Conference on Perinatal Diagnosis and Therapy, Budapest, 2004
    Prenatal diagnosis, phenotypic and obstetric characteristics of holoprosencephaly

    12th International Conference on Perinatal Diagnosis and Therapy, Budapest, 2004
    Ultrasound minor and major anomalies detected in fetuses with aneuploidies in second trimester

    12th International Conference on Perinatal Diagnosis and Therapy, Budapest, 2004
    Fetal cytogenetic analysis of fetuses conceived by intracytoplasmatic sperm injection
12th International Conference on Perinatal Diagnosis and Therapy, Budapest, 2004
How painful is amniocentesis?

Oligohydramniont és magzati kényszertartást okozó necrotizáló myomagöb
sikeres enucleatiója a terhesség 25. hetében
Magyar Nőorvos Társaság XXVI. Nagygyűlése, Pécs, 1998