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Prenatal diagnosis and further clinical characteristics of spina bifida

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ABSTRACT

Objective: To evaluate the major clinical features of pregnancies with spina bifida as well as to examine the diagnostic efficiency of ultrasonography based on autopsy. **Methods:** The investigations were made into the sample of 352 spina bifida diagnosed between 1990-2010 in the Semmelweis University. **Results:** The male: female ratio was 0.85. In 28.8% of all cases a positive obstetric, genetic or medical history was verified. The sensitivity of the maternal serum-AFP screening test was 52.1%. The majority of the cases were diagnosed before the 24th gestational week. Among the associated malformations out of the central nervous system special mentioning should be made of fetal pyelectasia, gastroschisis and pes equinovarus. The risk of recurrence was decreasing during the examined 29 years. Sonography proved to be a reliable method in diagnosing spina bifida. **Conclusion:** The malformation is more common among girls. Positive history is of great importance in the incidence of spina bifida. MSAFP tests are considered to be useful and necessary in screening, while sonography is the gold standard method in the diagnostics. We can confirm based on a big sample that the periconceptional administration of folic acid reduces the incidence and risk of recurrence of spina bifida.

1. Introduction

At the end of the 3rd gestational week, the neural folds gradually coalesce to form the neural tube whose cranial and caudal ends are initially open, but on day 24, both the anterior end (anterior neuropore) (Carnegie Stage 11) and, two days later, the posterior end (posterior neuropore) (Carnegie Stage 12) close [1, 2]. In the case of the above process being disturbed, a neural tube defect develops. This group of malformations may be divided into three major types known as spina bifida, anencephaly/exencephaly and encephalocele. Another, less common type of neural tube defect is iniencephaly.

As for etiology, this group of defects is of multifactorial origin, but its forms due to genetic mutation (e.g. Meckel-Gruber syndrome), teratogenic agents (e. g. valproates) and association with possible maternal disease (diabetes mellitus) are equally familiar [3-7].

Spina bifida develops due to the defective closure of the vertebral cavity along its midline (prevalence at birth is 0.23-4.13/1000; in Hungary 3.52-4.30/1000) [8-10]. Based on the size of the defect, rachischisis and lesions affecting only certain segments are distinguished, the former involving a cleft along the full length of the spine.

An association of spina bifida and hydrocephalus is often found, although the latter is regarded as being a separate entity according to the literature [11].

In the majority of the cases, spina bifida causes the newborn's death; in other cases irreversible damage (e.g. paralysis of the lower extremities, incontinence) of the newborn is expected. Criteria for selective surgery have been introduced, taking into account the severity, extent and location of the neural tube lesion, the presence or absence of associated malformations and the general condition of the newborn baby.

As spina bifida is among the most frequent malformations, we carried out our investigations to examine the characteristics of the background of this severe malformation in Hungary, as well as to compare with those of other publications emanating from different geographical origins. We attempted to analyse the demographic, obstetric and genetic factors influencing the characteristics of the malformation. We took the opportunity to evaluate the diagnostic accuracy of the ultrasound as well as to survey the effect of periconceptional folic acid supplementation on the prevalence and risk of recurrence of spina bifida.

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2. Materials and methods

We carried out investigations into the sample of 352 cases of spina bifida diagnosed at the 1st Department of Obstetrics and Gynecology of the Semmelweis University Medical School during the period 1990–2010. For the analysis of the cases we used informations concerning the demographic informations, history and outcome of pregnancy, as well as the results of examinations required in diagnosing spina bifida.

The computerized database provided detailed informations about the individual cases. The database was generated retrospectively after identifying genetic malformations. In addition to surveying the couples' major demographic details, we also had the opportunity to collect datas about the history (anamnesis concerning previous obstetrical events or complications, previous pregnancies with genetic malformations, as well as any kind of diseases affecting the gravida) diagnostics and outcome of the pregnancies during the investigation. Obstetric histories were regarded positive if previous miscarriage, missed abortion, premature birth, intrauterine death and ectopic pregnancy could be detected. Positive genetic history included any malformation that occurred in previous pregnancies. Medical history was regarded positive in case of previously known maternal diseases (e.g. diabetes mellitus, endocrine disorders etc.)

The diagnosis of spina bifida was based on the prenatal diagnosis of ultrasonography as well as the findings of the fetopathological examination. The diagnostic criterias were corresponded to that of the literature. (In case of a previous affected sibling diagnosed at our Department, the whole documentation, including the images of the ultrasound examination, photos of the fetopathological examination was accessible.). In Hungary since 1992 four screening ultrasound examinations are offered to low-risk pregnant women; in the 12–13th, 18–20th, 28–30th and 36–37th weeks of gestation. (This guideline determines the personal, technical and methodological conditions of sonographic examinations.) Earlier no protocol has prescribed the number and the date of the ultrasound screenings, though the ultrasound examination around the 20th gestational week was emphatically recommended. (Due to the different availability of sonography in the individual regions of Hungary, different dates of ultrasound examination are also possible.) Concerning the incidence of the associated malformations in the general population the Hungarian Malformation Registry served as a source.

During the 16th gestational week a maternal serum-AFP (MSAFP) examination is also performed to screen for fetal aneuploidy as well as neural tube defects. For the screening of fetal aneuploidies other important markers like beta-hCG, estriol and inhibin are also available; together with MSAFP and the value of nuchal transluciency (NT) during the 12th week ultrasound they render a reliable screening test of fetal trisomies.

The fetopathological investigations were usually carried out on the same, or following, day of abortion in the Fetopathological Laboratory of our Department.

Analysis of the risk of recurrence was one of the goals of the investigations; thus we also had the opportunity to gather indirect evidence concerning the preventive effect of periconceptional folic acid supplementation. Concerning the risk of recurrence we only considered cases of genetic origin. We could register the pregnancies in which a former spina bifida recurred again. Informations concerning the previously affected siblings were obtained through the reports of the fetopathological examinations and through final reports of medical treatments in hospital.

To compare the findings of ultrasonographic and fetopathological investigations, we distinguished three groups. Group 1 consisted of the cases in which the sonographic and foetopathological diagnoses coincided. Group 2 included pregnancies in which foetopathological and sonographic findings were essentially identical, and fetopathology provided additional information (different location; associated malformation) In Group 3, prenatal sonography and the post mortem investigation yielded completely different diagnoses (false positive sonographic diagnoses).

For statistical analysis, differences between groups were evaluated with a 2-tailed Student *t* test. For dichotomic parameters, the Fisher exact test was used. $P<0.05$ was considered statistically significant. Sensitivity was calculated as the proportion of affected individuals with a positive test result (affected with positive test/all affected).

3. Results

In the 352 cases of spina bifida, maternal and paternal median ages turned out to be 24.7 years (±4.64 years) and 30.8 years (±5.47 years), respectively.

If the order (number) of a given pregnancy is considered in view of the obstetrical history of pregnant women, it is clear that primigravidity ranks first (52.1%) in cases of spina bifida.

The proportion of male and female fetuses could be established from 338 cases. Males were involved in 46, while females were affected in 54% of the cases, the male-female ratio being 0.85 ($P>0.05$).

In 16.4% (58 cases) of all cases of spina bifida a positive obstetric, in 9.1% (32 cases) a positive genetic and in 3.3% (11 cases) a positive medical history was verified. (It should be mentioned, however, that the pregnant woman's positive medical history (diabetes mellitus, endocrine diseases, *etc.*) might also play a role in the etiology of the disorders in question, therefore it was essential to know the details. Among the 11 pregancies with positive medical history, in 7 cases (1.9%) diabetes mellitus occurred.

Maternal serum-alpha-fetoprotein examination is of importance in screening chromosome aberrations and neural tube defects. (AFP values fall in the physiological range of 0.9–2.5 MoM.) In the majority of the affected cases, maternal serum AFP levels have been available, as it can be seen in Table 2. In the cases of spina bifida the median values of maternal serum AFP are closer to the upper limit of the physiological range. The sensitivity of the screening test was around 52%.

Table 1
Parameters of MSAFP among the cases of spina bifida.

Maternal serum-AFP	Spina Bifida
No. of cases (n)	294
Mean (MoM)	2.33
SD	1.18
Median (MoM)	2.15
Minimum (MoM)	0.5
Maximum (MoM)	7.6
Sensitivity (%)	52.7

The diagram in Figure 1 allows for detection of the time of diagnosis in the defect in question. While the majority of cases (296 case; 84.1%) were diagnosed before the 24th gestational week, examples of diagnosing spina bifida at a later time could also be found (P<0,05). Among the 296 cases diagnosed before the 24th gestational week in 163 (55.1%) MSAFP value was above 2.5 MoM, while in 79 pregnancies (26.7%) between 2.0–2.5 MoM. In 26 cases (8.8%) MSAFP was under 2.0 MoM. In 28 cases the diagnosis was verifed without MSAFP result.(MSAFP value was available in 294 cases.)

In addition to recognizing the defect, ultrasonography also provides an opportunity to differentiate the anatomic locations of spina bifida (Table 3). In 75.8% of the cases of spina bifida, the lesion was situated in the lumbar region or caudal to that area. This means that the lower location of the malformation is significantly higher than the occurrence at higher segments (P<0.05).

Table 2
Anatomic location of spina bifida among the cases.

Anatomical location of spina bifida	N(%)
Cervical spina bifida	6 (1.8%)
Cervicothoracic spina bifida	3 (0.9%)
Thoracic spina bifida	14 (4.2%)
Thoracolumbar spina bifida	58 (17.4%)
Lumbar spina bifida	56 (16.8%)
Lumbosacral spina bifida	74 (22.3%)
Sacral spina bifida	112 (34.5%)
Rachischisis	7 (2.1%)

Ultrasonographic diagnostics allows for examining other malformations of the central nervous system accompanying spina bifida. The combination of spina bifida and anencephaly appears to be the most common association among the anomalies of the central nervous system, which corresponds to a ratio of 31.3% in spina bifida, respectively. The associated malformations other than those of the central nervous system include the ones affecting the extremities, urogenital system and abdominal/thoracic wall. Special mention should be made of fetal pyelectasia, pes equinonovarus as well as gastroschisis, as these malformations occur frequently. The incidence of these malformations together with spina bifida was significantly higher than their incidence in the general population (based on the Hungarian Malformation Registry) (P<0.05). Table 4 provides the details of associated, "non-central nervous system" malformations.

Table 3
Extracranial malformations associated with spina bifida.

Malformation		Spina bifida
Cardiovascular system		8 (2.3%)
	VSD	5 (1.4%)
	Univentricular heart	3 (0.9%)
Respiratory system		5 (1,4%)
	Hypoplastic lung	5 (1.4%)
Gastrointestinal tract		23 (6.5%)
	Oesophageal stenosis	8 (2.3%)
	Intestinal malrotation	12 (3.4%)
	Anal atresia	3 (0.9%)
Urogenital tract		38 (10.8%)
	Pyelectasis	24 (6.8%)
	Hydronephrosis	7 (2.0%)
	Megaureter	2 (0.6%)
	Dilatation of the bladder	2 (0.6%)
	Hypoplastic penis	2 (0.6%)
	Gonadal dysgenesis	1 (0.3%)
Endocrine system		2 (0.6%)
	Suprarenal aplasia	2 (0.6%)
Facial malformations		19 (5.4%)
	Cleft palate	7 (2.0%)
	Bulbar aplasia	2 (0.6%)
	Facial dysmorphism	10 (2.8%)
Malformation of the extremities		25 (7.1%)
	Talipes equinovarus	18 (5.1%)
	Polydactyly	3 (0.9%)
	Phocomelia	4 (1.1%)
Malformation of the thoracic/abdominal wall		24 (6.8%)
	Omphalocele	6 (1.70%)
	Gastroschisis	10 (2.8%)
	Diaphragmatic hernia	8 (2.3%)
Other malformations		11 (3.1%)
	Hygroma colli	5 (1.4%)
	Single umbilical artery	6 (1.7%)

Since neural tube defects are not frequently associated with chromosomal disorders, karyotyping was performed in only 81 cases of the sample. (In the past few years some data [11, 12] have linked abnormal folate metabolism with an increased risk of Down-syndrome, possibly through an increase in the rate of non-disjunction.) No pathological karyotypes were found in our sample of spina bifida.

As far as the outcome of pregnancies is regarded, in 83.2% of the cases an induced abortion, while in 12.5% of the cases-because of the gestational age- an induced premature delivery was performed. Five of the pregnancies (1.4%) with spina bifida ended in premature births, while mature babies were delivered in eight of them (2.3%). Owing to the location of the lesion, the prognosis was relatively favourable in these cases.

In our sample spina bifida was found in three multiple pregnancies. In one of them, spina bifida was diagnosed in both fetuses. In the remaining two cases the other twin (fetus "B" in both cases) proved to be healthy. In each cases termination of pregnancy was performed before the 24th gestational week.

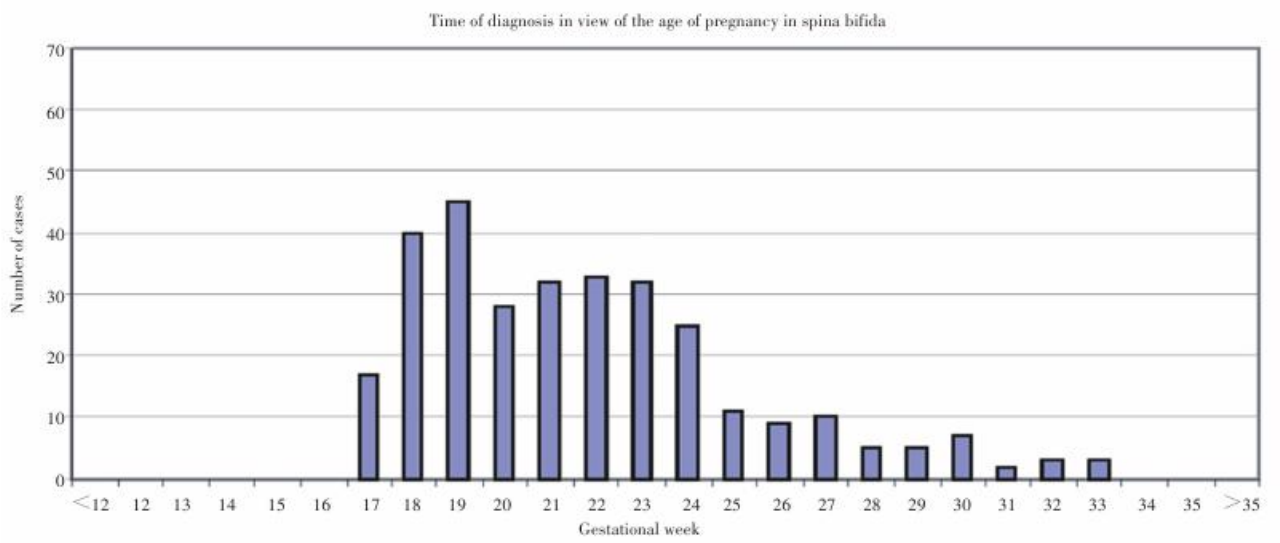

Figure 1. Time of diagnosis in spina bifida.

The risk of recurrence in five years periods has showed a clear and significant decrease; between 1979–1984 the risk of recurrence proved to be 3.8%, while in the last examined period until 2008 it was 1.8% ($P<0.05$) (Table 5).

Concerning the reliability of sonography in the diagnostics of spina bifida, it can be concluded that in about 78% of the cases with spina bifida prenatal ultrasonography and the fetopathological investigation revealed complete agreement with each other, in 18.5% of the cases there was a partial coincidence between these findings . In the latter group the diagnosis of spina bifida was verified but the anatomic type of the malformation was confused. In 3.5% of the cases a wrong diagnosis was given.

Table 4

The risk of recurrence of spina bifida in five years period between 1979 and 2008

The risk of recurrence of spina bifida	Percentage(%)
1979–1984	3.80
1985–1990	3.70
1991–1996	2.90
1997–2002	2.10
2003–2008	1.80

4. Discussion

The respective median values of maternal and paternal age at (24.7±4.6) and (30.8±5.4) years are in good agreement with those of Hall's, Hume's and Shaw's [12-14]. Our results confirm that parental age has no role in the occurence of spina bifida.

In our study, primigravidae were found to have the highest incidence of spina bifida, similarly to the publication by Mills [15].

Based on our results it can be concluded that spina bifida is more common amongst girls [14, 16, 17].

As it can be seen from the study, positive genetic, obstetrical and medical findings are of great importance in the incidence of spina bifida; not only positive genetic, but also positive obstetric history means a higher a predisposition to the malformation. Amongst the internal diseases diabetes mellitus probably plays a role worth mentioning in the etiology of neural tube defects and so in that of spina bifida, too. In 1.9% of our cases a maternal diabetes mellitus was known. This is 6–9 times higher than in the general population of pregnant women (0.2%–0.3 %). Confirming our findings, Main's studies highlighted that maternal diabetes mellitus could predispose fetuses to develop neural tube defects [18].

In maternal serum–AFP tests, the median values were in the range of (2.1±1.2) MoM, quite similar to the figures in the literature [6, 19-21]. The sensitivity of maternal serum AFP tests was found approximately 53% lower, than the results published by Nyberg and Rodriguez [19, 20]. (The sensitivity for detecting spina bifida can be improved by lowering the threshold to 2.0 MoM but this also results in a higher false-positive rate.) Although reliable to a limited extent, maternal serum–AFP tests are considered to be useful and necessary in screening neural tube defects and so spina bifida too [9, 22].

Although the majority of the cases involving spina bifida were diagnosed before the 24th gestational week, cases diagnosed later in this type of malformation were reported more frequently. In case of a cut-off value of MSAFP at 2.5 MoM, in 55% of the cases diagnosed before the 24th gestational week, sonography was performed with the knowledge of the positive screening test (MSAFP above 2.5MoM). Supposing a lower threshold at 2.0 MoM, almost 82% of the cases diagnosed before the 24th week would have been recognised by sonography after a positive screening test (MSAFP above 2.5 MoM). Summing up these

informations it would be worth of considering a lower cut-off value MSAFP at 2.0 MoM, in spite of the increasing number of false positive cases.

Analysing the anatomic locations of spina bifida, it can be concluded, that the malformation typically occurs at the lumbar or lower segments [23].

Owing to the high incidence of spina bifida in combination with anencephaly, the literature treats such cases as a separate entity [7, 24].

Among the malformations out of the central nervous system associated with spina bifida those of the extremities, the abdominal /thoracic walls, and the urinary systems are worth mentioning. As 95.7% of all cases have been terminated with induced abortion (before the 24th gestational week) or induced premature delivery (after the 24th gestational week), the associated malformations have been hardly influenced the outcome of the investigated pregnancies [23,25]. At the same time it can be concluded that the incidence of these malformations with spina bifida is significantly higher than in the general population.

It can be confirmed that there is no typical association between chromosome abnormalities and spina bifida [13]. Just as in cases of associated malformations out of the central nervous system, karyotype has also no significant influence on the outcome of pregnancies with spina bifida.

As far as the pregnancies in the sample were concerned, the majority of them were terminated by induced abortion or indiced premature delivery, however, pregnancies may be carried to term depending on the localisation of the defect. Criteria for selective surgery have been introduced, taking into account the severity, extent and location of spina bifida, the presence or absence of associated malformations.

Several studies were devoted to the various ways of primary prevention of neural tube defects earlier; in 1989 the first prospective, broadly based large mid-trimester study [26, 27] concluded that multivitamins with folic acid taken when planning pregnancy and for the first six weeks after conception provided about 70% protection against NTDs; in 1991, the UK Medical Research Council multi-country, randomized, double-blind intervention trial verified a 72% protective effect [28].

The decrease of recurrence risk in case of spina bifida is due to the regular folic acid intake of 0,8-1 mg/day in multivitamins 4 weeks before and 12 weeks after conception as a part of prenatal care in Hungary [29]. In Hungary since 1993 a guideline prescribes the periconceptionally recommended folic acid supplementation. Since that time there is a clear decrease of recurrence risk of neural tube defects [30]. Our data obtained from the sample of 29 years also confirm the results of previous publications, that the periconceptional administration of folic acid reduces the incidence and risk of recurrence of neural tube defects [15, 26, 28, 31]. Based on the above, folic acid supplementation can be regarded as the primary method of preventing this group of defects [32, 33].

In pregnancies with neural tube defects the complete agreement of sonography and autopsy was around 78%, which is similar to the findings of Sun [34]. In 18.5% of the cases the diagnosis of spina bifida was verified without the right anatomic location. It can be confirmed that in 96% of the cases spina bifida was diagnosed by sonography.

Based on our examinations it can be concluded that maternal and paternal age has no role in the occurrence of spina bifida. We confirmed, that spina bifida is more common amongst girls. The knowledge of the anamnesis is of great importance since positive genetic, obstetrical and medical history probably means a predisposition to spina bifida. In spite of its limited reliability maternal serum-AFP test is a necessary method in screening neural tube defects (and of course spina bifida), while sonography is the gold standard diagnostics in recognizing this malformation. (It is worth to consider to use a cut-off value of MSAFP at 2.0 MoM, as the sensitivity of the method would be improved.) The knowledge of the eventual associated malformations is mainly important in certain cases, which may also yield a good postnatal prognosis. Our data obtained from the sample of 19 years also confirm that the periconceptional administration of folic acid reduces the incidence and risk of recurrence of neural tube defects, and of spina bifida too. The significance of fetopathological examinations can be recognized in the evaluation of the efficiency of sonography in the diagnostics of the malformation. Based on the results of the autopsy a clear improvement in the accuracy of the ultrasound diagnostics of spina bifida can be confirmed.

Conflict of interest statement

We declare that we have no conflict of interest

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