Central nervous system anomalies diagnosed antenatally and post-delivery management

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ABSTRACT

الأهداف: معرفة نسبة تشوهات الجهاز العصبي قبل الولادة (CNS)، ونتائج ما يحصل بعد العلاج الجراحي للحالات التي يمكن علاجها جراحياً.

الطريقة: أجريت دراسة تحليلية بمراجعة ملفات الأمهات الحوامل بأجنة مصابين بتشوهات خلقية في الجهاز العصبي (CNS) و ذلك في مستشفى جامعة الملك عبد العزيز (KAUH) – جدة – المملكة العربية السعودية خلال الفترة من يناير 1997 حتى مارس 2005م. والنتائج التي تشمل ما حصل لهم الوفيات ما قبل وبعد الولادة، ونتائج ما حصل لهم بعد الجراحة التعديلية لما يصلح تعديله كعلاج، أو ترميمه.

النتائج: لقد شخصت 90 حالة تشوهات الجهاز العصبي قبل الولادة (CNS) وتأكد التشخيص بعد الولادة في 86 حالة. منها 41 حالة كانت عيوب في الأنبوب العصبي (47.7%)، 24 حالة انشقاق العمود الفقري مع استسقاء في الدماغ، 3 حالة فتق الدماغ، و 14 حالة مسخ الدماغ، كانت 36 حالة (41.9%) استسقاء فقط، 4 حالة مسخ الدماغ 4.65%، 3 حالة (3.4%) ضمور في الجمجمة، و 2 حالة (2.32%) أكياس في الدماغ. أجريت عمليات جراحية في 41 حالة، توفي من هؤلاء 6 حالة (14.6%)، بقي على قيد الحياة 26 حالة (63.4%) مع مضاعفات عصبية شديدة، فقد 6 حالة (14.6%) المتابعة، و عاشت 3 حالة (7.3%) بصحة جيدة لمدة المتابعة.

خاتمة: نسبة تشوهات الجهاز العصبي (CNS) تتشابه مع نسبتها في دول العالم. إن إنشاء وإيجاد خطط لتقليل نسبة التشوهات سيكون مفيداً لمنع حصول هذه التشوهات التي عادة ما تؤدي إلى إعاقة ومعاناة شديدة حتى بعد العلاج الجراحي.

Objectives: To find out the prevalence of the central nervous system anomalies (CNS) and the outcome after surgical correction of operable defects.

Methods: This is a retrospective review of all cases diagnosed antenatally with CNS anomalies in the Department of Obstetrics and Gynecology at King Abdulaziz University Hospital (KAUH), Jeddah, Kingdom of Saudi Arabia from January 1997 to March 2005, and their outcome including perinatal deaths and postoperative outcome following surgical correction carried out as treatment or palliative.

Results: Ninety CNS anomalies were diagnosed antenatally, and 86 were confirmed postnatally. Forty-one (47.7%) were neural tube defects (NTDs) (24 were spina bifida associated with hydrocephalus, 3 encephalocele, 14 anencephaly), 36 (41.9%) were hydrocephalus, 4 (4.65%) holoprosencephaly, 3 (3.4%) microcephaly, and 2 (2.32%) with brain cysts. Of the 41 cases that were operated, 6 (14.6%) died, 26 (63.4%) survived with severe neurological sequelae, 6 (14.6%) lost follow-up, and 3 (7.3%) did well for the period of follow-up.

Conclusion: The prevalence of CNS anomalies is comparable to worldwide prevalence. The NTDs are important component of these anomalies, and implementation of strategies to decrease the rate of these anomalies would be beneficial to prevent them as they carry a high rate of handicap and suffering, even after surgical correction.

Saudi Med J 2010; Vol. 31 (3): 257-261

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Received 7th December 2009. Accepted 23rd February 2010.

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Central nervous system anomalies including hydrocephalus and neural tube defects (NTDs) are common major congenital anomalies worldwide, and NTDs are the second most common after cardiac

malformations.[1] They can occur as part of a genetic syndrome or constellation of abnormalities.[2] Isolated NTDs occur in 1.4-2 per 1,000 pregnancies.[1] Chumas et al[3] reported that the prevalence of congenital and infantile hydrocephalus is between 0.48 and 0.81 per 1,000 births (live and stillbirths),[3] and a significant percentage of these patients will be left with persistent neurological deficits. In the United Kingdom and Ireland, the number of shunt operations is estimated to be 3500-4000 a year by the Cambridge based UK Shunt Registry. In the United States, approximately 125000 shunt procedures are carried out annually at an estimated cost of 100 million dollars.[3] The NTDs are a major cause of stillbirth, neonatal and infant death, and lifelong severe handicap. With treatment, 80-90% of infants with isolated spina bifida survive with varying degrees of handicap.[2] Most importantly, NTDs are among the few birth defects for which primary prevention is possible; prenatal screening and diagnosis is widely available, and prenatal therapy is being investigated.[1] The NTD birth rate in Ontario (live births and stillbirths) decreased from 10.6 per 10,000 births in 1986 to 5.3 per 10,000 in 1999. The decline in NTDs was thought to be due to increased intake of folic acid at the time of conception.[4] This study was carried out to evaluate the prevalence of CNS anomalies among births delivered at King Abdulaziz University Hospital (KAUH), and the outcome of infants with these abnormalities who are candidates for surgery.

Methods. Since January 1997, a fetal registry of congenital abnormalities diagnosed antenatally has been started, and the cases of this study have been recruited from this registry since it started, up to the end of March 2005. Ethical approval had been obtained from the bioethical and research committee of KAUH. Inclusion criteria included: any suspected CNS abnormalities on ultrasound, if on a subsequent investigation the anomaly was thought to be another system anomaly, it was excluded from the study, or if the patient was not delivered in the hospital. The maternal demographic data included: age, gravidity, parity, weight, height, consanguinity, previous history of abortion, stillbirths (SB), neonatal deaths (NNDs), and history of previous malformations. Gestational age was calculated from the first day of the last menstrual period, or confirmed by ultrasound. Significant maternal illness for example, diabetes, hypertension, and use of medication had been recorded. The mode of delivery was recorded. The neonatal outcome included: birth weight, gender, Apgar score, resuscitation, neonatal intensive care unit (NICU) admission, SB, NND (early or late). The type of the anomalies was classified as: hydrocephalus, ventriculomegaly, anencephaly, encephalocele, spina bifida (meningomyelocele), microcephaly, and holoprosencephaly. Hydrocephalus types included: aqueductal stenosis, Arnold Chiari malformation (ACM), Dandy Walker malformation (DWM), and corpus callosum agenesis. The diagnosis of these cases was made by antenatal ultrasound, and confirmed by neonatal examination and ultrasound. Postmortem examination is not carried out routinely in cases of neonatal deaths or stillborns. The termination of pregnancy for non-lethal anomalies is not practiced in this country. Earlier spontaneous losses are not registered even if discovered to be anomalous, so these are not included in the study. The timing of postnatal intervention had been specified as either carried out in the neonatal period, or delayed to a 6-12 months period. Intervention included either placement of a shunt, or a repair of meningomyelocele. Postoperative complications included: fever, infection, respiratory complications, seizures, or convulsions, jaundice, and necrotizing enterocolitis (NEC). Delayed complications included: CNS abnormalities and neurologic sequelae, urinary system complications, musculoskeletal abnormalities, eye complications, and finally even death. These babies had been followed regularly at the pediatric, or neurosurgical clinic according to the disabilities and need for surgical intervention.

Results. Ninety cases had been diagnosed antenatally to have CNS abnormalities. The total number of deliveries during that period was 29,519 and the total number of births was 30,016. The incidence of CNS anomalies was 0.29%, or 3 per 1000 births. The types of anomalies diagnosed are presented in **Table 1**. Of the total prenatal ultrasound diagnosis, 83 were confirmed by a postnatal ultrasound (92.2%), 3 were normal, and one was misdiagnosed as microcephaly, but postnatally was anencephaly, one was diagnosed as cystic hygroma, which post delivery was found to be large encephalocele. Another prenatal diagnosis of microcephaly was not confirmed after delivery, but the newborn died with multiple congenital anomalies including sacrococcygeal teratoma, and it was excluded from the study. One case diagnosed as ventriculomegaly antenatally was microcephaly following delivery with associated hiatus hernia and intestinal malrotation, which was operated upon, but the baby died at the age of 3 months. The corrected incidence will be 86 per 30,016 births, or 2.87 per 1000 births. The maternal demographic data included a mean age of 29.5 years, 64 were ≤5 parity, and only 22 had a parity of >5. Consanguinity was common with a first degree relative in 30 women (34.9%), and 10 women being from the same tribe (11.6%). Of the women in the study, 9 (10.5%) had diabetes (frank and gestational). This compares with a prevalence of

gestational diabetes in a Saudi population of 11%.[5] Hypertension was uncommon, and it was found only in 2 (2.3%) women. Most mothers took prenatal vitamins, but it was not specified, if it included the recommended dose of folic acid. Of the total 86 cases with CNS anomalies; 46 (53.5%) had associated anomalies other than CNS anomalies, including cardiac, renal, gastro-intestinal, musculoskeletal, facial and genital anomalies (**Table 2**). The type of hydrocephalus was antenatally diagnosed in 24 patients only (24/36 [66.67%]). These were: 8 cases ACM, 5 aqueductal stenosis, 7 DWM, and 4 corpus callosum agenesis. Thirty-nine babies died as a complication of their disease' severity (20 cases(51.3%), or because of associated anomalies (19 cases (48.7%). Thirteen babies had anencephaly; 5 of them were born as stillbirths at variable gestational ages, as the termination of pregnancy had some ethical consideration and not carried out routinely for these cases, 7 died immediately following delivery, one of these was a case of holorachischisis. The 14 anencephaly died 34 days post delivery. Five cases were not operated on because of inoperable condition (one case brain cyst, one brain atrophy associated with brain cyst, one hydrocephalus with complex anomalies, one trisomy 18, and one severe hydrocephalus with no brain tissue), and they survived until the end of the study. One case was diagnosed as hydrocephalus due to aqueductal stenosis, but it was mild and did not progress, and the baby did not require surgical intervention during the follow-up period of 23 months as the development was normal (the final diagnosis was arrested hydrocephalus). Hydrocephalus and meningomyelocele were the 2 major indications for surgical intervention. Forty-one babies were operated on with either shunt only for isolated hydrocephalus (20 cases) or shunt, and repaired for hydrocephalus and associated meningomyelocele (13 cases), or repair only (5 cases) for meningomyelocele, and repair followed by shunt if complicated by postoperative hydrocephalus (3 cases). Most of the cases had been operated on immediately following delivery, or during the neonatal period after stabilizing the baby, but a few had the surgery later according to the condition of the newborn. Of the babies operated on, 6 (6/41 [14.6%]) died as LNNDs, or infant deaths due to complications. Two were transferred to another hospital for management, as at the time of delivery there was lack of availability of either a NICU bed, or lack of ventilator. One of them died at the age of 5 months, and the other survived until the end of the study. Another 2 patients were transferred to other hospitals for the same reasons, but their outcome was not known because they lost follow up (**Table 3**). Most babies who survived (33 cases) the initial neonatal period had neurological sequelae. Twenty-six (78.8%) had severe neurological sequelae including paraplegia and neurogenic bladder, or mental retardation, delayed milestones, and so forth. Four (12.1%) lost follow up, and hence, had unknown outcome. Three babies (9.1%) did well, and had normal

Table 1 - Types of the neurological abnormalities (N=86).

Types of anomaly	n	(%)
Hydrocephalus	36	(41.9)
Holoprosencephaly	4	(4.7)
Neural tube defects (n=41)		
Anencephaly	13	(31.7)
Holorachischisis	1	(2.4)
Enencephalocele	3	(7.3)
Spina bifida + hydrocephalus	24	(58.5)
Brain cysts	2	(2.3)
Microcephaly	3	(7.3)
Total	**86**	**(100)**

Table 2 - The neurological abnormality with other associated congenital anomalies.

Types of anomaly	n	(%)
Hydrocephalus + ventriculomegaly, n=36	24	(66.7)
Holoprosencephaly, n=4	2	(50.0)
Neural tube defects (n=41)		
Anencephaly, n=13	2	(15.4)
Holorachischisis, n=1	1	(100.0)
Enencephalocele, n=3	2	(66.7)
Spina bifida, n=24	11	(45.8)
Brain cysts, n=2	2	(100.0)
Microcephaly, n=3	2	(66.7)
Total=86	**46**	**(53.5)**

Table 3 - Outcome of the babies with central nervous system abnormalities.

Outcomes	n	(%)
Stillbirths	7	(8.1)
Early neonatal deaths	25	(29.0)
Late neonatal deaths	4	(4.7)
Infant deaths	9	(10.4)
Transfer to another hospital, n=4	2	(4.7)
Operated on	41	(47.7)
Operated on and survived	33	(38.4)
Operated on and died, n=6	4	(7.0)
Operated and transferred	2	(2.3)
Non-operated on and survived	6	(7.0)
Non-operated and died	39	(45.4)
Operated and intact survival	4	(4.7)
Non-operated and intact survival	1	(1.2)
Non-operated on and survived with complications	2	(2.3)

Table 4 - The outcome of babies with central nervous system anomalies operated upon.

Type of surgery	Total number of patients operated	Total number of patients died (%)	Number of patients survived with sequelae (%)	Number of patients survived without sequalae (%)
Shunt procedure	20	4 (20.0)	11 (55)	2 (10)
Meningomyelocele repair	3	1 (33.3)	0	2 (66.7)
Encephalocele repair	2	0	2 (100)	0
Shunt & meningomyelocele repair	12	0	12 (100)	0
Meningomyelocele repair then shunt	4	0	4 (100)	0

growth and development for the period of follow up that ranged between 15-45 months) (**Table 4**).

Discussion. It had been shown that the outcomes of NTDs and CNS abnormalities are associated with poor outcome. Anencephaly is incompatible with life; with treatment, 80-90% of infants with spina bifida survive with varying degrees of disability.[1] The prenatal diagnosis in this study was confirmed in 94% of the cases, which is similar to that reported by D'Addario et al[6] (positive predictive value was 93.1%). The prevalence of CNS anomalies in this series was 3 per 1000 births. This series included 43 NTDs (50%) of the total CNS anomalies. The incidence of NTDs will be 0.14% or 1.4 per 1000 births. This compares to 8-10 per 10,000 or 0.8-1 per 1000 in the United States,[6] 1.5 in 1000 in Izmir Turkey,[7] but it is lower than the rate of 4 in 1000 in another report from Turkey,[9] and highest in the world from China with 138.7 per 10,000 or 13.8 per 1000 births.[10] Although the prevalence is similar in this study to other countries, the actual prevalence of the country is not available because of a lack of fetal registry of congenital anomalies, except for sporadic institutions or tertiary care facilities, and the rate could be higher. Another limitation is that anomalous fetuses lost before 20 weeks are not registered. Thirty-four (56.7%) babies with hydrocephalus were not associated with NTD. Of these, 20 (58.8%) died because of severity of the disease and associated anomalies, while 14 of them were operated upon. Of the babies with hydrocephalus not associated with NTDs, the postoperative mortality was 28.6% (4 of 14), this is much higher than the reported postoperative mortality of 5-15% reported by Chumas et al,[3] and this could be related to late diagnosis and more severe disease. Few babies lost follow up after the first postoperative visit. Two babies survived with normal neurological function for a period of follow up of 15-16 months (14.3%), the other 5 (35.7% of the total and 50% of survivors) had neurological sequelae including bladder and bowel dysfunction, and they had been followed for up to 20-52 months. This compares with a rate of 60% reported by Chumas et al in their previous study.[3] Futagi et al[11] reported the neurodevelopmental outcome of 38 babies operated upon during the neonatal period, and showed that 3 (7.9%) were normal, borderline intelligence in one patient (2.6%), mental retardation in 7 (18.4%) patients, and motor disturbance in 27 (71.1%) patients.

This series of CNS abnormalities included 43 NTDs including 13 cases with anencephaly, one case of craniorachischisis, and 29 spina bifida. All anencephalic fetuses died as expected, 8 cases (27.6%) of spina bifida died in the neonatal period because of significant associated anomalies, the other 21 of the spina bifida patients were operated upon, 19 survived with variable neurological sequelae (95%). The period of follow up varied from 20-71 months, only one case did not show up after the 2 months visit, and one case was followed to the end of the study (6 months), and it was Walker Warburg syndrome with a poor outcome. The mortality rate of these cases compares favorably to a rate of 40.8% reported by Preis et al[12] for live born babies with myelomeningocele in Poland. Most of these patients had both repair and shunt at the same time, but 9 had repair carried out, and of these 4 (44.4%) required a shunt procedure later on because of developing hydrocephalus. Davis et al[13] reported on the long term follow up of children with meningomyelocele over 43 years, and concluded that for all patients alive at age 16, a significant decrease in survival probability after age 34 was found for individuals with shunted hydrocephalus, compared to those without a shunt (p=0.03), although childhood survival was not related to shunt status. *In-utero* repair of myelomeningocele had been shown to decrease the incidence of shunt-dependent hydrocephalus,[14] although 54% who underwent operation *in-utero* required the placement of a ventriculoperitoneal shunt before the age of one year.[15] Danzer et al[16] showed in his study that in contrast to postnatally repaired patients, *in-utero* repaired fetuses showed significant reversal of hindbrain herniation. From 1994-2003, 4 US medical centers performed more than 200 hysterotomy repairs of fetal myelomeningocele, and the observational data resulted from these centers suggested a potential for a decrease in the requirements of early shunting of children operated prenatally. Even so, these data did not demonstrate a

functional improvement in outcome compared with the traditionally treated children with spina bifida. In July 2001, the Management of Myelomeningocele Study (MOMS), had been designated to answer the question of whether *in-utero* repair of spina bifida results in enough benefit to the baby to warrant the maternal, fetal, neonatal, and economic risks incurred.[17] *In-utero* repair is still considered as investigational until the final answer is reached by the team of the MOM study.

The limitation of this study was that it was a retrospective review of data, and the period of follow up was short to allow comment on the functional abilities of these children.

In conclusion, studies are needed to prenatally identify common anomalies in this country, and to be registered at a local fetal registry for each province of the Kingdom. Efforts can then be unified to look at possible preventable causes, and find the best measures to decrease them. This may include implementation of strategies to decrease the rate of NTDs, which carry a high rate of handicap and suffering, even after surgical correction. These should include campaigns to educate teenagers at schools, or at universities of the importance of periconceptional folic acid supplementation. The government should study the implementation of fortification of food with folic acid, although some papers had shown that fortification of food with folic acid may carry a risk to un-intended group, where folic acid may be harmful.[19] Physicians and health and social professionals should spend more time and effort on educating the public on the risk of consanguineous marriages, and the importance of early antenatal care.

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