The incidence and spectrum of central nervous system malformations in newborns over a decade (2001-2010) in the Central Region of Saudi Arabia

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ABSTRACT

الأهداف: دراسة طيف التشوهات الخلقية للجهاز العصبي المركزي عند الأطفال السعوديين حديثي الولادة والتي وُثقت بالأشعة الطبقية أو أشعة الرنين المغناطيسي خلال 10 سنوات، ومقارنتها بما هو مدون في حيثيات الأدب الطبي.

الطريقة: لقد قمنا في هذه الدراسة باسترجاع بيانات الأطفال حديثي الولادة ممن دخلوا إلى قسم الرعاية المركزة للأطفال حديثي الولادة بمستشفى الرياض العسكري، الرياض، المملكة العربية السعودية وذلك خلال الفترة من يناير 2001م إلى ديسمبر 2010م، والذين أُجريت لهم الأشعة الطبقية أو أشعة الرنين المغناطيسي للجهاز العصبي المركزي. لقد تم استبعاد الأطفال المولودين خارج المستشفى، وكذلك الأطفال الذين تعرضوا للاختناق أثناء الولادة، والأطفال الخدج.

النتائج: لقد تم إجراء 849 فحص شعاعي للدماغ خلال هذه الدراسة، وأظهرت النتائج إصابة 248 طفل بتشوهات خلقية للجهاز العصبي المركزي. وكان 58 طفل (23.4%) مصاباً بمتلازمات خاصة مصحوبة بتشوهات الجهاز العصبي المركزي. وظهر خلل الرفاء (المنشقة السنسنية) عند 42 طفل (16.9%) 17 منهم كان قحفياً وفي 25 كان شوكياً. وأُصيب 30 طفل (12.1%) باستسقاء الدماغ، فيما أُصيب 31 طفل (12.1%) بالتشوهات الخلقية للقشرة المخية، وفي 20 منهم كانت التشوهات ناتجة عن ارتحال الخلايا الدماغية. لقد شملت تشوهات المخيخ والحفرة الخلفية للدماغ 44 طفل (17.7%)، وظهرت متلازمة دندي ووكر عند 15 طفل ومتلازمة جوبرت عند 12 طفل. وظهرت تشوهات الدماغ الأمامي في 39 طفل (15.7%)، 29 منهم أُصيبوا بتشوهات الصوار الأعظم، وأُصيب 12 طفل باندماج مقدم الدماغ. وشُخص اختلال الأوعية الدموية لدى 4 أطفال فقط.

خاتمة: أثبتت هذه الدراسة ظهور طيفاً كبيراً من التشوهات الخلقية في الجهاز العصبي المركزي وقد تم توثيقها بطرق الأشعة الحديثة.

Objectives: To study the incidence and spectrum of central nervous system (CNS) malformations confirmed by computerized tomography (CT), or magnetic resonance imaging (MRI) in a Saudi newborn population of Riyadh over a 10-year period, and to compare our findings with those in the published literature.

Methods: This is a retrospective analysis of prospectively collected data on all inborn babies admitted to the Neonatal Intensive Care Unit in Riyadh Military Hospital, Riyadh, Kingdom of Saudi Arabia that underwent CT or MRI of the brain and spine from January 2001 to December 2010. Out born babies, babies who sustained birth asphyxia, and premature babies were excluded from the study.

Results: During the study period, 849 imaging studies were carried out, and from these 248 babies with CNS malformations were identified. Specific syndromes associated with CNS malformations occurred in 58 (23.4%). Dysraphism was found in 42 babies (16.9%) (25 spinal and 17 cranial). Hydrocephalus was present in 30 (12.1%), cortical malformations occurred in 31 (12.5%), which was dominated by abnormal cell migration in 20. Cerebellar and posterior fossa abnormalities were diagnosed in 44 (17.7%), Dandy-Walker syndrome in 15, and Joubert syndrome in 12. Prosencephalic pathology was seen in 39 (15.7%), commissural abnormalities in 29, while there was holoprosencephaly in 12. Vascular malformations were found in 4 babies (1.4%).

Conclusion: This study showed a wide spectrum of malformations, with all CNS malformations confirmed by advanced imaging techniques.

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With the recent advances in obstetrics and neonatal care, the perinatal mortality rate has dropped significantly in most countries in the world including the Kingdom of Saudi Arabia (KSA).[1,2] In developed countries, congenital malformations are the leading cause of neonatal mortality.[3] In a previous study from the same institute, congenital malformation comprised 36% of the causes of neonatal death.[2] In KSA, consanguineous marriages still ranges between 50-90% in various part of the kingdom.[4,5] Due to religious beliefs, termination of pregnancy is not allowed except when the mother's life is in danger.[6] In addition, larger family size and other environmental factors could have contributed to the high rate of congenital malformations found in the kingdom. The Saudi Armed Forces personnel represent a good cross section of the Saudi society. The Riyadh Military Hospital (RMH) is a tertiary care hospital with an annual number of deliveries of just over 10,000 live births (LB). The Neonatal Intensive Care Unit (NICU) is a level 3B unit, which has an annual admission rate exceeding 1,000 newborns. All live born babies with serious structural malformations are admitted to the NICU for management and parental counseling. We aimed to study the spectrum and incidence of the central nervous system (CNS) malformations confirmed by computed tomography (CT), or magnetic resonance imaging (MRI) of the CNS in babies that were admitted to the NICU over the past decade. This was compared to what is reported in the literature from within and outside the kingdom.

Methods. We used our NICU database (NICUDB) to identify babies with CNS malformations. The NICUDB contains all prospectively collected information on babies admitted to the unit. At discharge, the medical staff complete a specially designed data sheet that contains all the demographic characteristics of the babies, their medical diagnoses, treatment, and procedures. The database contains special entries with regard to CNS malformations, CNS imaging, neural tube defects (NTD's), specific syndromes, brain vascular abnormalities, chromosomal anomalies, and multiple congenital malformations that are without a definite diagnosis. The mother's age, parity, mode of delivery, previous neonatal deaths, history of previous abnormal babies, and current pregnancy complications are also recorded. It was conducted from January 2001 to December 2010 This study is a retrospective analysis of prospectively collected data on all inborn babies admitted to the NICU in RMH, Riyadh, Kingdom of Saudi Arabia that underwent CT or MRI of the brain and spine. All babies who fulfilled the previous NICU DB criteria entries were selected. Our Obstetric Department's policy stated that all women who will attend the antenatal clinic should at first presentation, be booked for ultrasound screening examination at 16-20 weeks of gestation, to detect any congenital malformations. It is the NICU protocol to admit all babies with any antenatally, or postnatally identified CNS malformations that needed imaging studies. These were tabulated with the patient's name, hospital number, and gender in order to avoid duplications. Babies included in the study underwent either a CT, or MRI of the brain and spine, or both. The CNS malformations detected on the antenatal ultrasound were verified by postnatal imaging studies. Some babies have had more than one imaging study to elucidate the diagnosis, or for follow up. All gestations were included, and reports of the CT and MRI of the brain and the spine during the study period were reviewed and correlated with the clinical diagnoses. We used the classification adopted by Volpe[7] for general CNS malformations, and the classification proposed by Barkovich et al[8] for cortical malformations. Babies were classified according to the major underlying CNS pathology (primary pathology), although some of them did have multiple malformations, involving more than one area of the CNS (associated defects). Malformation was grouped into the following: congenital hydrocephalus (CH); dysraphism or NTD's; cerebellar and posterior fossa malformations; cortical lesions; prosencephalon pathology; brain vascular anomalies; and specific syndromes associated with CNS defects. Each infant was counted once for the main or "primary" lesion, but for the type of the malformation, both primary and associated defects were counted. Out born babies, babies who sustained hypoxic ischemic encephalopathy, and babies with CNS complications secondary to their prematurity were excluded.

The statistical software for the Centers for Disease Control and Prevention (Epi Info 2011 version 3.5.3) was used for data entry and analysis.[9] Chi square test and descriptive statistics were used to analyze the data.

Results. During the study period, there were 94,210 LB recorded, and of these, 8,140 (8.6%) were admitted to the NICU. A total of 849 CT and MRI of the brain and spine were performed on babies admitted to the NICU. In 379 babies, no congenital CNS malformations were found, and 248 babies with CNS malformations underwent a total of 470 imaging studies. In the 248 babies with CNS malformations, 51% were male, and 174 (70%) survived to discharge. This represented 2.63/1000 LB delivery, and 30.46/1000 LB NICU

Table 1 - Demographic characteristics of mothers and babies during the study period in Riyadh Military Hospital, Kingdom of Saudi Arabia.

Characteristics	Mean ± standard deviation	Range
Birth weight (grams)	2624 ± 802	570-5000
Male, n (%)	127 (51.0)	23-42
Gestation (weeks)	37.4 ± 3.3	1-506
Survived to discharge, n (%)	173 (70)	15-49
Hospital stay (days)	55.5 ± 81	0-17
Maternal age (years)	28.87 ± 6.6	
Parity	2.62 ± 2.66	
Diabetes, n (%)	29 (11.7)	
Toxemia of pregnancy, n (%)	1 (0.4)	

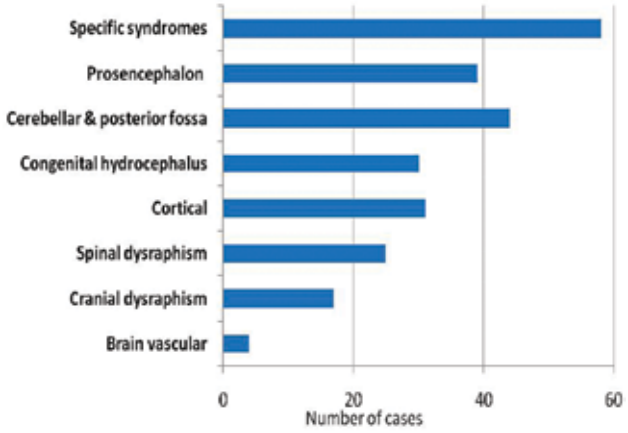

Figure 1 - Spectrum of central nervous system malformations in 248 babies with central nervous system malformations.

admissions. **Table 1** shows the mothers' and babies' demographic characteristics, parity, maternal diabetes, and toxemia of pregnancy. The spectrum of the CNS malformations is shown in **Figure 1**. Fifty-eight cases (23.4%) with specific syndromes associated with CNS malformations represented the largest group, while brain vascular malformations were seen in 4 (1.4%) cases only. In the group of specific syndromes, there were 10 cases with chromosomal abnormalities (trisomy 13 in 3, trisomy 18 in 4, trisomy 21 in 1, and others in 2). The rest represented a diversity of rare syndromes as shown in **Table 2**. There were 42 (16.9%) cases of dysraphism (25 spinal and 17 cranial) with an overall incidence of 0.44/1000 LB, and 5.16/1000 LB admission to the NICU. There were another 8 cases of dysraphism as part of specific syndromes (5 Meckle Gruber, and one each in Oeis, Jarco Levens, and Caudal regression), and 2 associated with Dandy-Walker malformation, and these were not included in the calculation of the NTD's incidence. **Figure 2** shows the incidence of NTD at RMH between 1998 to 2010. Cortical malformations were found in 31 babies (12.5%), predominated by abnormal cell migration in 20, including 6 with Walker-Warburg syndrome. Abnormal cell organization was seen in 4, white matter disease was diagnosed in 4, and a miscellaneous group of disorders in 5, and more than one cortical pathology was seen in 2 babies. **Table 3** shows details of the isolated and cortical malformations associated with other CNS malformations. There were 30 (12.1%) babies with HC, in which 19 (63.3% [13 were males and 6 females]) is due to aqueduct of Sylvius stenosis or obstruction. In another 7 (23.3%), this was due to other factors (2 congenital intraventricular hemorrhage, 2 arachnoid cysts, and one each for cerebral hematoma, narrow foramen of Monroe, narrow foramen of Magnum). In 3 babies, no cause was demonstrated. One baby has communicating HC. The spectrum of malformations in the cerebellum and the posterior fossa were found in 44 babies (17.7%). This group is dominated by Dandy-Walker malformations in 15 (34.1%) and Joubert's syndrome in 12 patients (27.3%). **Table 4** shows the primarily cerebellum and posterior fossa malformations, and those whose cerebellum and posterior fossa pathology represent a part of their CNS malformations.

There were 39 babies (15.7%) with prosencephalic malformation (**Table 5**). Some of the babies have more than one pathology as demonstrated by their imaging studies. Alobar was seen in 5, and semilobar holoprosencephaly was seen in 7 babies. Another 4 were associated with chromosomal abnormalities (trisomy 13 in 3, and one microdeletion of P18), and further 2 seen with specific syndrome (Probocis cycopia, Cyclops syndrome). Commissural anomalies were found in 64 babies, in 29 it was an isolated pathology, and in 35 it was associated with other CNS malformations. Total agenesis of corpus callosum (CC) in 41 babies ([64%] 21 males, 20 females), and partial agenesis in 23 ([36%] 13 males and 10 females). Specific syndromes were associated with commissural anomalies in 14 babies (21.8%). Colpocephaly was found in 26 babies, and in 21 it was associated with commissural pathology, while in 5 it was isolated. Cerebral vascular malformations were seen in 4 babies (1.4%), one each in: vein of Galen malformation; congenital prosencephalic cyst; cavernous sinus thrombosis; and cerebral infarction.

Discussion. The annual incidence of CNS malformations ranges between 1.66 per 1000 LB in 2002, and 4.56 per 1000 LB in 2007 with an overall incidence of 2.63 per 1000 LB. An incidence of 2.63/1000 LB is almost similar to the 3/1000 LB, reported by Mansouri[10] from the Western province, and lower than 9.6/1000 LB cited by Al-Jama[11] from the Eastern Province of KSA. The major difference between the studies from

Table 2 - Central nervous system (CNS) malformations associated with rare syndromes in the studied group of newborns in Riyadh Military Hospital, Kingdom of Saudi Arabia.

Syndrome	CNS malformations
Adams Oliver	Hydrocephalus
Aicardi x2	Corpus callosum agenesis
Apert	Corpus callosum agenesis
Baller Gerold	Corpus callosum agenesis, colpocephaly
Caudal regression	Thoracolumber myelomeningocele
Chondrodysplasia punctata	Cortical calcification
CMV	Intracranial calcification
Cross	Cortical atrophy
Cutis verticis gyrate x3	Cortical polymicrogyria
Cyclops	Alobar holoprosencephaly
deBarsay	Cortical calcification and atrophy
Di George	Paucity of white matter
Idiopathic infantile arterial calcification	Hydrocephalus
Jarco Levens	Thoracolumber myelomeningocele, Arnold Chiari malformation
Kabouki	DWM, Cerebellar hypoplasia
Arthrogryposis congenita multiplex x4	Lissencephaly, DWM
Sturge Weber x4	Liptomeningeal angiomatosis
Jeune thoracic dystrophy	Cerebellar hypoplasia, cortical hamartoma
MDF x2	Microgyria, cortical atrophy
Morquio's disease	Colpocephaly
Neu Lexa	Lissencephaly
Oeis complex	Spina bifida, cortical atrophy
Ohtahara	Spina bifida, cortical atrophy
Spina bifida, cortical atrophy	Pachygyria
Perlam	Cortical atrophy
Proboscis cyclopia	Alobar holoprosencephaly
Proteus	Cortical atrophy
Retinoic acid embryopathy	DWM
Schinzel Giedion x2	Cerebellar and vermian hypoplasia
Simpson Golabi	Corpus callosum dysgenesis
Valporate embryopathy	Focal cortical thickening
Zellweger x3	Pachygyria, cortical atrophy
Zlotogora-Ogur	Corpus callosum dysgenesis
Tuberous sclerosis x2	Cortical tuberous
Suspected thalidomide embryopathy	Demylination, cerebral infarction

CMV - Cytomegalovirus, MDF - multiple dysmorphic features, DWM - Dandy-Walker malformation
x - indicates the number of babies with similar syndrome

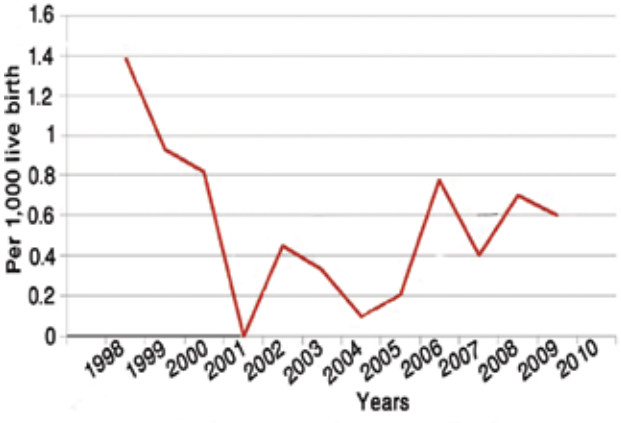

Figure 2 - The incidence of neural tube defects in Riyadh Military Hospital, Riyadh, Kingdom of Saudi Arabia (1998-2010).

the different parts of KSA and our study is the rate of NTD: 0.73/1000 LB in Mansouri study;[10] 7.61/1000 LB in Al-Jama report;[11] 0.82/1000 LB in El-Awad and Sivasankaran;[12] and 1.6/1000 LB in Thaliji et al[13] report, while it is 0.44/1000 LB in our series. This could be partly explained by the different methodologies of the studies, especially the inclusion and exclusion criteria, the regional difference in incidence of NTD, and the improved standards of living. The combined number of NTD and hydrocephalus in Mansouri's study[10] was 2.6/1000 LB, while in this study they represent 1/1000 LB. Rajab et al[14] from the Sultanate of Oman reported an incidence of 1.25/1000 LB for NTD, and 1.69/1000 LB for the combined incidence of NTD and HC, while Golalipour et al[15] from the Islamic Republic of Iran reported an incidence of 3.4/1000 LB for NTD, which

Table 3 - Spectrum of cortical malformations in 31 of 248 babies with central nervous system (CNS) malformation.

Cortical pathology	Primary†	Associated*
Abnormal cell migration		
Lissencephaly	8	2
Pachygyria	4	6
Hetrotopia	2	1
Walker-Warburg	6	0
Abnormal cell organization		
Cortical dysplasia	0	2
Polymicogyria	2	2
Schizencephaly	2	0
Abnormal cell proliferation		
Hemimegalencephaly	0	1
White matter disorders	4	3
Cortical atrophy	4	16
Others	1	10
Total	**33**	**43**

†some babies have more than one malformation, *cortical pathology associated with other CNS malformations

Table 4 - Spectrum of cerebellum and posterior fossa malformations in 44 of 248 babies with central nervous system malformations.

Cerebellar pathology	Primary†	Associated*
Dandy-Walker malformation	15	7
Joubert's syndrome	12	0
Cerebellar hypoplasia	6	11
Meckle Gruber syndrome	5	0
Vermian hypoplasia	4	2
Arachnoids cyst	3	6
Arnold Chiari malformation		
Type 1	0	1
Type 2	0	12
Pontocerebellar hypoplasia	2	0
Total	47	39

†some babies have more than one malformation, *cerebellar pathology associated with other central nervous system malformations

Table 5 - Spectrum of prosencephalic malformations in 39 of 248 babies with central nervous system (CNS) malformation.

Prosencephalic pathology	Primary†	Associated*
Holoprosencephaly		
Semilobar	7	1
Alobar	5	2
Lobar	0	3
Commissural anomalies		
Agenesis of corpus callosum	21	20
Partial agenesis of corpus callosum	8	15
Colpocephaly	14	12
Septo-optic dysplasia	1	0
Total	**56**	**53**

†some babies have more than one malformation, *prosencephalon pathology associated with other central nervous system malformations

is higher than in the current study. Czeizel and Revesz[16] from Budapest reported an incidence of 2.95/1000 LB for NTD, and 3.71/1000 LB for combined NTD and congenital hydrocephalus. The rising trend in the incidence of NTD at RMH since 2003 as shown in **Figure 2** is of concern. Although it is still relatively low at 0.6/1000 LB in 2010, it needs to be monitored closely.

The use of prophylactic folic acid in KSA is still irregular, patchy, and most of the time the women start to take folic acid only after confirmation of her pregnancy.[17] This rise is in contrast to an earlier report by Safdar et al[18] from the Western province of Saudi Arabia indicating a declining incidence in NTD. In the group of cerebellum and posterior fossa malformations, there were 22 cases of Dandy-Walker anomaly (2.3/10,000 LB), which is much higher than 0.1/10,000 LB reported by Ohaegbulam and Afifi[19] from the Northern region of KSA, and 0.4/10,000 LB as reported by Blaser[20] from USA. Twelve infants were diagnosed to have Joubert's syndrome represent a 1.27/10,000 LB, this is higher than what is reported from the European countries and USA at 0.1 /10,000 LB.[21,22] Arnold Chiari type 2 malformation is less common in our series at 1.27/10,000 LB than 4.4/10,000 LB as reported by Moore[23].

Primary or "isolated" cortical malformations were seen in 31 babies representing 12.5%, and so far, none of the studies from within the KSA and the Middle East to our knowledge reported any incidence with regards to the "isolated" cortical pathology. Commissural anomalies were seen in 64 babies representing 25.8% of the entire group, and 6.8/10,000 LB. This is higher than what Glass et al[24] reported at 1.8/10,000 LB, and Paul et al[25] at 2.5/10,000 LB. Total agenesis of the CC was found in 64% in our series, while it comprised 47.6% in Bedeshi et al's study[26]. Other CNS malformations associated with total agenesis of CC were found in 20 (57.1%) babies (10 with specific syndrome, 5 with cortical lesions, cerebellar lesions in 3, and singly with hydrocephalus and NTD) compared to 10 (33%) babies (8 with cortical lesions and cerebellar malformations in 2) as reported by Bedeschi et al[26]. Holoprosencephaly was diagnosed in 18 babies (1.9/10,000 LB) similar to what was reported in the literature at 1-1.4/10,000 LB.[27,28] Chromosomal anomalies associated with holoprosencephaly were reported between 9-40%,[27-29] and in our series it is 22%.

Important limitations of this study should be noted. It did not include stillbirths and postmortem examinations that are not allowed in KSA, except in medico-legal cases. Including still-births could have raised the number of cases and postmortem examinations would have led to a more precise diagnosis, especially with regard to cortical pathology. In addition, cases that is not detected by the antenatal ultrasound screening examination, and showed no clinical manifestation

at the immediate neonatal period would have been missed.

We believe an overall incidence of 2.63/1000 LB for CNS malformations is lower than the actual incidence due to the above-cited limitations. An incidence of approximately 4/1000 LB would probably be more accurate as seen in the later years of the study because of better antenatal ultrasound detection rate. A multicenter collaborative, prospective study is needed to accurately estimate the true incidence of CNS malformations in KSA. In addition, with the modern modalities of neuroimaging coupled with molecular cytogenetic testing, better understanding, and precise diagnosis of CNS malformations can be carried out. Preimplantation diagnosis and counseling is the way forwards in most of these rare but serious CNS malformations, especially as the issue of termination remains unresolved.

In conclusion, this study demonstrated a high incidence, and a wide spectrum of CNS malformations that are confirmed by neuroimaging. The incidence of NTD has been shown to be rising over the last 5 years, and needs close monitoring. Specific syndromes associated with CNS malformations were the largest group (23.4%) followed by cerebellar and posterior fossa malformations (17.7%). This study suggests the need for a large multicenter prospective study coupled with molecular genetics analysis for these malformations. Molecular genetics analysis will lead to better parental counseling and management.

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