International Journal of Clinical and Diagnostic Pathology

ISSN (P): 2617-7226
ISSN (E): 2617-7234
www.patholjournal.com
2021; 4(3): 93-98
Received: 09-05-2021
Accepted: 12-06-2021

Dr. Padmaja Korti
Associate Professor,
Department of Pathology,
Kamineni Academy of Medical Sciences and Research Centre
L. B. Nagar, Rangareddy
Hyderabad, Telangana, India

Dr. Alka Kalgutkar
Ex-Professor and Head,
Department of Pathology,
Lokmanya Tilak Municipal Medical College and Hospital
Sion, Mumbai, Maharashtra, India

Corresponding Author:
Dr. Padmaja Korti
Associate Professor,
Department of Pathology,
Kamineni Academy of Medical Sciences and Research Centre
L. B. Nagar, Rangareddy
Hyderabad, Telangana, India

Congenital CNS malformations in pediatric autopsies and surgical specimens

Dr. Padmaja Korti and Dr. Alka Kalgutkar

DOI: https://doi.org/10.33545/pathol.2021.v4.i3b.394

Abstract
Aim: The aim of the present study was to analyze congenital central nervous system (CNS) malformations from paediatric autopsies and from surgical specimens, to recognise, record, categorise the congenital CNS malformations and to study its association with various maternal and fetal factors.
Materials and Methods: This is both prospective (June 2009 to May 2011) and retrospective study conducted during period of two and half decades i.e. from 1987 to May 2011 in a tertiary care hospital. Cases were selected from both pediatric autopsies and surgical specimens as per inclusion and exclusion criteria. Pediatric autopsy was conducted as per standard protocol after obtaining consent from parents.
Results: Out of 3492 pediatric autopsies, the CNS malformations were seen in 58 cases and out of 5639 pediatric surgical specimens, 85 were of CNS anomalies. In autopsy study neural tube defects (NTD), 20 cases (34.48%) were the most common followed by congenital hydrocephalus, 14 cases (24.14%). In surgical specimen study all were NTD except for one neuroenteric cyst.
Conclusion: Neural tube defects were the most common CNS anomalies; majority of which could be surgically treated. CNS anomalies are associated with preterm births, low birth weight and younger maternal age.Although radiological investigations have high sensitivity in diagnosing CNS malformations, autopsy findings are essential to arrive at a definitive diagnosis.

Keywords: CNS malformations, paediatric autopsy, congenital anomalies

Introduction
Malformations of central nervous system are among the most common, yet most devastating of congenital anomalies [2]. The important proven etiological factors of congenital malformations are single mutant gene, chromosomal abnormalities, major environmental factors like maternal infections, maternal exposure to alcohol and ionizing radiation [1]. Although data is available regarding the incidence of individual CNS malformations in living children, similar data is lacking in an autopsy population [2]. Autopsy is one of the most valuable techniques which aid in establishing a precise diagnosis for accurate genetic counselling of the parents. However this process of analysing a mixture of complex anomalies is faced by problems of nomenclature which can be solved by a pathogenetically oriented and practical classification. To the best of our knowledge, such data is meagre in Indian literature, which prompted us to take up this study. A survey of congenital CNS malformations from series of autopsy cases and from surgical specimen so as to include those CNS malformations which are surgically treated were studied to recognise, record, to categorise the congenital CNS malformations and study its association with various maternal and fetal factors.

Materials and methods
It is both prospective (June 2009 to May 2011) and retrospective study conducted during period of two and half decades i.e. from 1987 to May 2011 in a tertiary care hospital. Cases selected were from both pediatric autopsies and surgical specimens as per inclusion and exclusion criteria.

Inclusion Criteria
1. Age: Upto 15 years
2. Congenital Malformation of Central nervous system i.e. both Brain and spinal cord abnormalities

Exclusion Criteria

1. Age: > 15Years
2. Abnormalities secondary to post natal CNS infection and tumor.

After obtaining consent from parents, complete autopsy was done with detailed external examination and anthropometric measures. The internal examination was performed with the evisceration of the block, all systems and organs were dissected and sections for microscopic examination was taken and processed by routine paraffin embedding and stained with haematoxylin and eosin stain. Photographs were taken and clinical information along with radiological details was collected from the accompanying pathology request form. In retrospective cases similar information were gathered by retrieving previous autopsy records.

The surgical specimens received in our department during above period were selected as per inclusion and exclusion criteria and were examined grossly and microscopically. Required clinical and radiological details obtained from histopathology request form. In retrospective cases above information was gathered by retrieving previous histopathological report and indoor papers. Before start of study, consent obtained from the ethical committee of the institute.

Data collected was analyzed and the abnormalities were classified according to the embryonic development of the central nervous system [1]. The CNS malformations were assessed in relation to gender, age, birth weight, gestational age and maternal age. The associations with malformations of other organs or congenital syndromes were noted.

Results

We examined 3492 pediatric autopsies performed in tertiary care hospital during the years from 1987 to May 2011. There were 58 cases with central nervous system malformations. The frequency CNS malformations were 1.66% of total pediatric autopsies. Age wise distribution of total cases shown in the table 1 and spectrum of central nervous system malformations observed shown in table 2.

Table 1: Age wise distribution of cases in autopsy study

Age groups	Cases	
	Numbers (n)	%
Still births	11	18.97
Neonates	34	58.62
One month to 15 years	13	22.41
Total	58	100

CNS malformations were maximum among neonates (58.62%), followed by stillbirths (SB) (18.97%). 5 cases presented at age of 1-5 years and only one case presented beyond 5 years of age.

Gender distribution of CNS malformations

Female preponderance was observed with 36 cases (62.07%) girls (G) and 22 cases (37.93%) boys (B). So overall boys to girls ratio was 1:1.6. The gender ratio in SB, neonates and infants was 1:10, 1:1.3 and 1:0.8 respectively.

Table 2: Spectrum of central nervous system malformations

CNS malmormations		Number
Neural tube defects	Anencephaly	02
	Craniospinal rachischisis	01
	Encephalocele	06
	Meningomyelocele	10
	Spina bifida occulta	01
	Total	20(34.48%)
Congenital hydrocephalus		14(24.14%)
Prosencephalon anomalies	Holoprosencephaly	02
	Agenesis of corpus callosum	02
	Total	04(6.90%)
Disorders of neuronal proliferation and migration	Microcephaly	07
	Tuberous sclerosis	02
	Porencephaly	01
	Multicystic encephalopathy	01
	Hydrancephaly	01
	Total	12(20.69%)
Malformations of brainstem and cerebellum	Dandy walker malformation	03
	Arnold chiary malformation	01
	Total	04(6.90%)
Miscellaneous	Meckelgruber syndrome	01
	Down syndrome	01
	Acephaly	01
	Crouzon syndrome	01
	Total	04(6.90%)
Grand total		58

In the present study, the neural tube defects (NTD), 20 cases (34.48%) were the most common followed by congenital hydrocephalus, 14 cases (24.14%). In NTDs, meningomyeloceles, 10 cases (50%) were most common followed by occipital encephaloceles, 6 cases (30%). Lumbosacral was the most common site of meningomyeloceles followed by lumber region. There were 25 cases of hydrocephalus, 7 cases associated with NTDs were classified as NTDs and 4 cases associated with malformations of brainstem and cerebellum were classified as latter malformations. Of the 14 cases of isolated congenital hydrocephalus, the etiology could not be ascertained in the 11 cases (78.57%). In the remaining 3 cases, one case each of aqueductal stenosis (Figure 1),

congenital primary cerebral neuroblastoma and congenital choroid plexus papilloma were noted. In the disorders of neuronal proliferation and migration, the microcephaly was the most common (n = 7, 58.33%) followed by tuberous sclerosis (n=2, 16.67%). In malformations of brain stem and cerebellum included two different entity, one case of Arnold- Chiari malformation (Figure 2) and three cases of Dandy- Walker malformations. Twenty six years old mother delivered term male baby with birth weight of 2600 gm had hydrocephalus. The cause as Arnold-Chiari malformation was diagnosed on MRI. Baby died in the late neonatal period due to shunt complication. On autopsy cerebellum showed stretched cone shaped vermis.

CNS malformations in relation to gestational age

In cases with CNS malformations frequency of preterm births (58.62%) were more common than full term births (41.38%). Preterm births observed in various CNS malformations were as follows, 65%, 71.43%, 58.33%, 50% in NTD, congenital hydrocephalus, disorders of neuronal proliferation and migration, malformations of brainstem and Cerebellum respectively. Full term babies were predominant in cases with prosencephalon malformations. In the miscellaneous group, the cases of Down's syndrome and Crouzon syndrome were term born and Acephaly and Meckcle Gruber syndrome were preterm born.

CNS malformations in relation to birth weight

Most cases were born with low birth weight (67.24%), normal birth weight was observed in 32.76% of cases. Among the low birth weight babies (LBW) 2 cases (3.45%) were in the birth weight of 1001-1500gms. 13 (22.41%) cases belong to 1501-2000 gms and 24 cases (41.38%) were of birth weight ranging from 2000 to < 2500gms.

The frequency of LBW babies in various CNS malformations were as follows NTD (65%), congenital hydrocephalus (71.43%), disorders of neuronal proliferation and migration (75%), malformations of brainstem and cerebellum (66.67%). In prosencephalon anomalies there were equal number of LBW and normal birth weight babies.

CNS malformations in relation to maternal age

There were differences among maternal age specific frequency of CNS malformations. The highest (34.48%) was in an age < 20 years and lowest (12.07%) was in the age ≥ 30 years.

31.03%, 22.41% of cases were observed in the maternal age groups of, 20-25 and 25-30 yrs respectively. In all forms of CNS malformations the maternal age was < 25 yrs except in congenital hydrocephalus the maternal age was > 25 years.

Table 3: Association of CNS malformations with other organs/ system malformations

CNS Malformations	N (%)
Isolated CNS malformations	40(68.97%)
CNS malformations with other organ/ system anomalies	14(24.14%)
Syndromes	04 (6.90%)
Total	**58 (100%)**

Associated abnormalities in cases with neural tube defects (n=8)

- Anencephaly with bilateral adrenal hypoplasia-Two cases
- Craniospinal rachischisis with bilateral adrenal hypoplasia, omphalocele and fused hypoplastic kidneys with bilateral lung hypoplasia-One case
- Thoracic menigomyelocele with bilateral congenital talipusequinovarus, and bilateral cystic renal dysplasia with bilateral lung hypoplasia --One case.
- Spina bifida occulta with unilateral renal agenesis with bilateral lung hypoplasia - One case
- Encephalocele with cleft lip and palate and bilateral cystic renal dysplasia with hypoplasia of bilateral lung---- One case
- Encephalocele with cleft lip and palate--- Two cases

Associated abnormalities in cases with microcephaly (n=4)

- Cleft lip and palate--- One case
- Imperforate anus, bilateral hypoplasia of kidney and lung --- One case
- Omphalocele--- One case
- Bilateral cystic renal dysplasia with hypoplasia of lung--- One case

Congenital hydrocephalus with cleft lip and palate, transposition of great vessels, left diaphragmatic hernia and malrotation of gut --- One case

Dandy-Walker malformation with left diaphragmatic hernia-One case

CNS Anomalies and Syndromes

One case each of Meckel-Gruber syndrome, TRAP syndrome, Crouzon syndrome and Down syndrome was found.

Twenty years old mother delivered a preterm male baby with birth weight 2200gms which was diagnosed on antenatal USG as anencephaly. At autopsy baby had an occipital encephalocele along with polydactyly and infantile polycystic kidney disease constituting Meckel-Gruber syndrome (Figure 3).

Eighteen years old mother delivered a term male neonate weighing 2600gms had craniofacial dystosis and craniosynostosis was diagnosed as Crouzon syndrome.

A Downs syndrome male baby with birth weight 2100gms born to 32 years old mother at term had lumbosacral meningomyelocele.

Twenty-six years old mother delivered preterm twin babies, one of them was still born female with birth weight 2000gms had acephalia (Figure 4) and acardia as a result of twin reversed arterial perfusion (TRAP) syndrome.

Surgical specimen study results

We analysed 5639 paediatrics surgical specimens from 1987 to May 2011, out of which 85 (1.51%) were of specimens of CNS anomalies. CNS malformations consisted mainly of neural tube defects (NTDs) and a solitary case of neuroenteric cyst (Table 4).

Table 4: Surgically treated CNS malformations

Anomalies		Numbers	Percentage
Neural Tube Defects	Meningomyelocele	45	52.94
	Meningocele	16	18.82
	Encephalocele	13	15.29
	Spina bifida occulta	06	7.06
	Tethered cord syndrome	04	4.71
Other	Neuroenteric Cyst	1	1.18
Total		85	100

Among the NTDS, most were of spinal dysraphism at various levels of spine (Figure 5) and remaining were Occipetalencephalocele (Figure 6). The most common site

of spinal dysraphism was lumbosacral (47.89%) followed by lumber region (26.76%). Meningomyelocele were the commonest and most common site was lumbosacral (46.67%) followed by lumber region (24.44%). The smallest was 1cm in diameter and largest being 8 cm in diameter. All cases of encephalocele were seen in occipital region. The smallest was 2cm and largest was 10cm in diameter. Fifteen cases of NTDs were associated with hydrocephalus, in that 3 were case of occipetalencephalocele and 12 were of meningomyelocele.

Age and Gender distribution.

Out of 85 cases, 32 were neonates (37.65%), 35 were infants (41.18%), 12 cases (14.12%) were in the age group of 1-5 years. Only 6 cases presented beyond 5 years of age. Female preponderance was observed with 51 cases (60%) girls and 34 cases (40%) boys. So overall boys to girls ratio was 1:1.5. The gender ratio in neonates and infant was 1:1.5 and 1:1.7 respectively.

Child and maternal factors associated with CNS malformations

The frequencies of preterm births (58.82%) were more common than full term births (41.18%). The frequency of cases of CNS malformations with low birth weight (n=56, 65.88%) was higher than that with normal birth weight (n=29, 34.12%).Among the low birth weight babies, 6 cases (7.06%) were in the birth weight of 1001-1500gms. 20 cases (23.53%) cases belong to 1501-2000gms and 30 cases (35.29%) were of birth weight ranging from 2000 to < 2500gm.

Almost equal frequency of CNS malformations was observed in the maternal age groups of < 20 yrs (40%) and 20-25 yrs (43.53%). Lowest frequency (3.53%) was observed in mothers aged ≥ 30 years.

Neuroentericsyst

A 2 month old male infant born to 24 years old mother at term presented with inability to move upper limbs since birth. On MRI, diagnosed as congenital syringobulbia and underwent operation for the same. On histopathological examination diagnosed as neuroenteric cyst (Figure 7). It was a rare case of intramedullary neuroenteric cyst. Approximately 90% of neurenteric cysts are located in the intradural/extramedullary compartment, while the remaining 10% are divided between an intradural/ intramedullary or extradural location [10].

Discussion

Congenital malformations are major causes of perinatal morbidity and mortality worldwide [3]. Reported incidences of malformations vary considerably depending on the definition and classification of malformations, the source of the diagnosis and the sampled population.

Although the present study encompasses cases of lethal CNS malformations from autopsy records and those treated surgically, it does not reflect the true incidence of CNS malformations. However it emphasizes the common non-lethal CNS anomalies which can be surgically treated.

Autopsy Study

Of the total paediatric autopsies evaluated, 15.41% had congenital malformations and 1.66% had CNS malformations. It is in concordance with similar study done by De Noronha L *et al.* (2.69%) and Froehlic *et al.* [4] (2.7%).The frequency of individual CNS malformations in autopsy studies by different authors is as follows (Table 6)

Table 6: Frequency of individual cns malformations in autopsy Studies [2, 3]

Anomalies	H. Pinar *et al.*	De Noronha L *et al.*	Present study
NTD	165 45.5%)	96 (61.15%)	20 (34.48%)
Congenital hydrocephalus	45 (12.4%)	30 (19.48%)	14 (24.14%)
Microcephaly	24 (6.61%)	7 (4.46%)	7 (12.07%)
Holoprosencephaly	20 (5.51%)	7 (4.46%)	2 (3.45%)
Agenesis of corpus callosum	15 (4.13%)	2 (1.27%)	2 (3.45%)
Dandy-walker syndrome	7 (1.93%)	1(0.6%)	3 (5.17%)
Arnold-chairi malformation	18 (4.96%)	3 (1.91%)	1(1.72%)
Others	72 19.83%)	11 (7.01%)	9 (15.52%)

Age distribution

In the present study CNS malformations were more frequent among neonates (59.62%) followed by SB (19.30%). It is in concordance with De Noronha L *et al.* [3] study and Pinar H *et al.* [2] study. In De Noronha *et al.* L study 69% of CNS malformation cases were neonates and 54% were SB and in Pinar H *et al.* study it was 64.74% and 35.26% respectively. In the study by Sobanice LM *et al.* [5], the newborns were predominated, representing 64% of children with CNS malformations but these authors did not include stillbirths. Verma *et al.* [6] claims that CNS malformations are more frequent among stillborns

Gender distribution

Females predominated among CNS malformation with 62.07% of cases and boys to girls ratio (B: G) was 1:1.6. De Noronha L *et al.* [3] and Sobaniec *et al* [5] also found the predominance of females with 54.14% and 57% respectively.

Frequency of CNS malformation in relation to gestational age and low birth weight

The frequency of preterm births (58.62%) and low birth weights (67.24%) was higher in cases with CNS malformations. It is in concordence with Brown WR *et al.* [7] study, who found the rate of preterm birth was higher (33.1%) in subject with congenital brain defects than infants without defects (9.3%). This suggests that babies with brain defects are predisposed to be born preterm. The reverse, that preterm birth predisposes to congenital brain defects, is not plausible.

Frequency in relation to maternal age

We observed inverse relation between maternal age and frequency of CNS malformations. The highest frequency (34.48%) was in the maternal age group <20 years and lowest (12.07%) were in maternal age group ≥ 30 years. A clinical study carried out by Ana Gaardiolaetal [8] also found association between CNS malformation and young maternal age. But Gustav Granroth *et al.* [9] found high parental age turned out to be risk factor in the group of all CNS defects, mainly owing to the subgroup of hydrocephaly. We also observed higher maternal age only in cases of congenital hydrocephalus.

Association of CNS malformations with that of other organs / systems

In the present study, 14 cases (24.56%) of CNS malformations were associated with malformation of other organ/ system and 4 cases with syndromes. It is lower than

that observed by De Noronha L *et al.* [3] who observed 41% of CNS malformations were associated with that of other organ/ systems and 30 cases were of syndromes. Pinar H *et al.* [2] carried out chromosomal analyses in CNS anomalies cases and found major CNS malformations such as hydrocephalus and microcephaly were associated with large number of MCA syndromes. Pinar H *et al.* [2] observed 6 cases of meningomyeloceles with chromosomal abnormalities. We found a case of Down syndrome with meningomyelocele. Pinar H *et al.* [2] observed acephalia in 4 cases of TRAP syndrome and one of them also was associated with menigomyelocele.

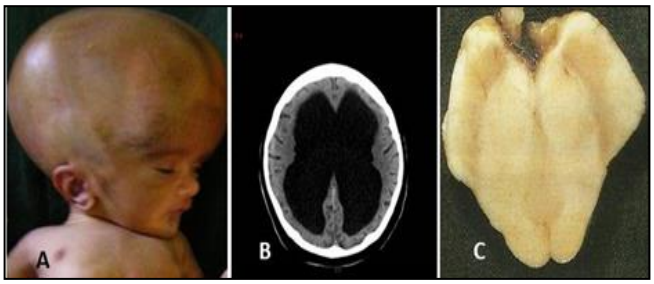

Fig 1: A. Congenital hydrocephalus in a neonate, B. MRI revealed aqueduct stenosis, C. Slice of mid brain showing aqueductal stenosis.

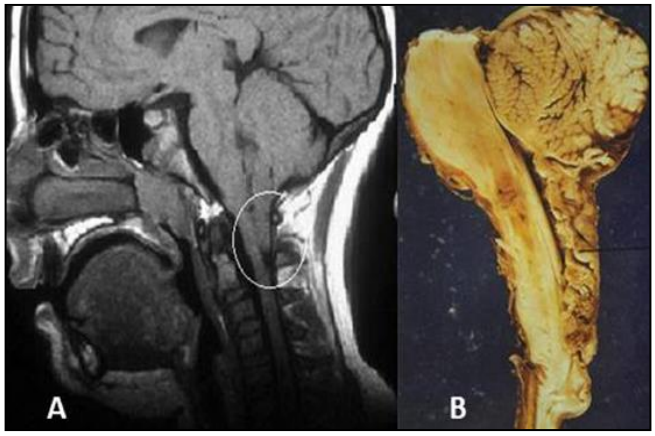

Fig 2: A. Arnold- Chairi malformation, MRI showing tonsillar herniation, B. Median section through cerebellum and brain stem showing stretched cone shaped vermis.

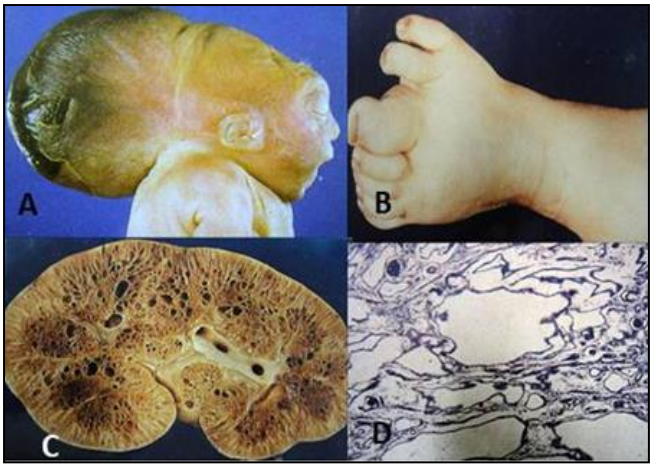

Fig 3: Meckle- Gruber syndrome. A. Occipetal encephalocele. B. Polydactyly involving the medial aspect of the left foot. C. Cut surface of Infantile Polycystic kidney. D. Microphotograph of Infantile Polycystic kidney.

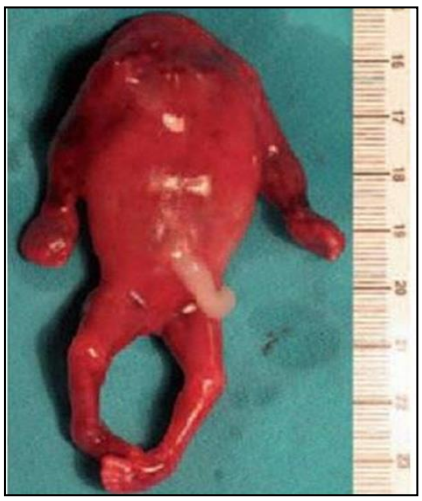

Fig 4: TRAP Syndrome- Fetus with acephaly

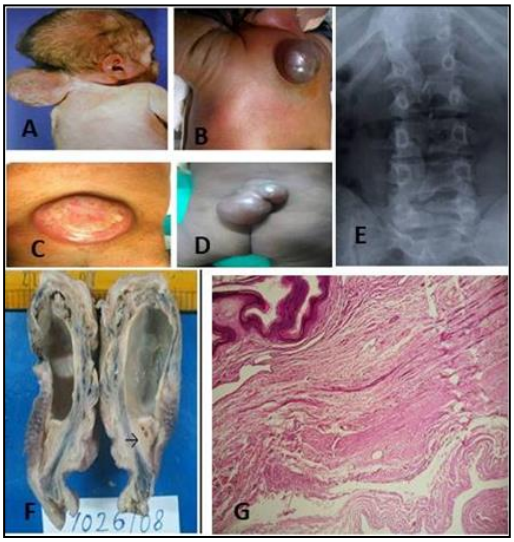

Fig 5: Various levels of Spinal dysraphism. A. Cervical region. B. Thoracic region. C. Lumbar region. D. Lumbosacral region. E. Plain x-ray, AP view, of the lumbosacral spine with posterior fusion defects of the laminae in a case of spina bifida. F. Cut surface of specimen of meningomyelocele. G Microphotograph of Meningomyelocele.

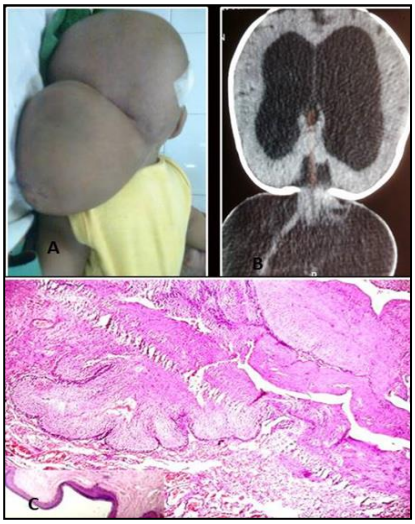

Fig 6: A. Clinical picture of Occipetal encephalocele. B MRI showed Occipetal encephalocele with hydrocephalus. C. Microphotograph of encephalocele.

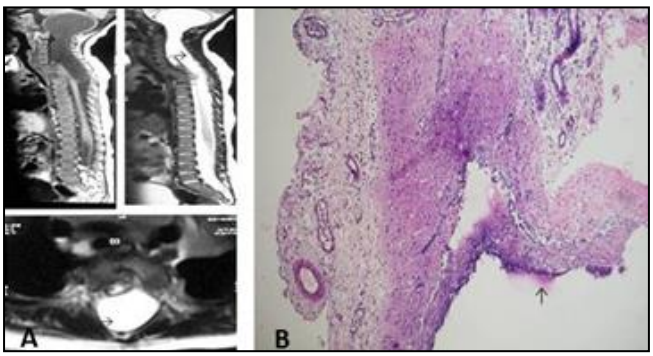

Fig 7: A. MRI showing neuroenteric cyst as an intramedullary cyst extending from medulla to D5 vertebra (arrow). B. Microphotograph of neuroenteric cyst, showing cyst lined by ciliated columnar epithelium (arrow).

Conclusion

Neural tube defects were the most common CNS anomaly. Maximum cases were seen in the neonatal period and that too in girls. CNS anomalies were associated with preterm births, low birth weight and younger maternal age.Although radiological investigations have high sensitivity in diagnosing CNS malformations, autopsy findings are essential to arrive at a definitive diagnosis.

References

1. Larroche JC, Razavi FE. Central nervous system malformations. In: Wigglesworth JS, Singer DB, editors. Text book of fetal and perinatal pathology. 1st edition. Boston: Blackwell scientific publications 1991.
2. Pinar H, Tatevosyants N, Singer DB. Central nervous system malformations in a perinatal/neonatal autopsy series. Pediatr Dev Pathol 1998;1(1):42-8.
3. De Noronha L, Medeiros F, Martins VD, Sampaio GA, Serapião MJ, Kastin G, *et al.* Malformations of the central nervous system: analysis of 157 pediatric autopsies. ArqNeuropsiquiatr 2000;58(3B):890-6.
4. Froehlich LA, Fujikura T. Congenital malformations in perinatal, infant and child deaths. In: Nishimura H, Miller JR, editors. Methods for Teratological Studies in Experimental Animals and Man. Tokyo: IgakuShoin 1969, 167-194.
5. Sobaniec-LM, Sobaniec W, Sulkowska M, Sulkowski S, Kulak W. Morphologic analysis of congenital central nervous system malformations in children from the first of life dying in the years 1986-1990. Pol MerkurLekarski 1996;1(5):334-6.
6. Verma M, Chhatwal J, Singh D. Congenital malformations--a retrospective study of 10,000 cases. Indian J Pediatr 1991;58(2):245-52.
7. Brown WR. Association of preterm birth with brain malformations. Pediatr Res 2009;65(6):642-646.
8. Guardiola A, Koltermann V, Aguiar PM, Grossi SP, Fleck V, Pereira EC. Neurological congenital malformations in a tertiary hospital in south Brazil. ArqNeuropsiquiatr 2009;67(3B):807-11.
9. Granroth G, Hakama M, Saxén L. Defects of the central nervous system in Finland: I. Variations in time and space, sex distribution, and parental age. Br J PrevSoc Med 1977;31(3):164-70.
10. Lippman CR, Arginteanu M, Purohit D, Naidich TP, Camins MB. Intramedullary neurenteric cysts of the spine. Case report and review of the literature. J Neurosurg 2001;94:305-9.