Childhood Brain Lesions: 15 years Experience of King Abdulaziz University Hospital (1995-2010)

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Abstract: Pediatric age brain lesions can be of neoplastic and non-neoplastic nature, the latter include: congenital malformations, inflammatory processes, vascular and cystic lesions. One of most concerning brain pathology in childhood age is CNS tumors. Malignant brain tumors are the second most common type of pediatric cancer after leukemia. Cancer of the brain and central nervous system comprised 17% of malignancies in children younger than 20 years of age . In Saudi Arabia childhood CNS cancer accounted 11.3% of all childhood cancers. The current study presented the experience of King Abdulaziz University Hospital regarding Childhood Brain Lesions diagnosed over 15 years period (1995 to 2010) considering frequency, morphological pattern and the demographic data (age distribution and gender) of these lesions and further compared the findings with the national and international experience. A retrospective study conducted using a computerized search of the archives of Pathology Department at King Abdulaziz University Hospital in Jeddah; from 1995 tell 2010 to retrieve all the brain cases inclusive of all brain regions. In 15 years period 71 cases (25.1%) out of total brain lesions (283 cases) were childhood brain lesions. Non-neoplastic lesions were 40.8% and neoplastic lesions were 59.2%. Congenital malformations (23.9%) were the commonest non-neoplastic brain lesions, while neuroepithelial tumors ranked first among neoplastic lesions and accounted for 25.4% of childhood brain lesions (CBL) in the study. The astrocytic tumors comprised the majority of the glial tumors (94.4%) with mean age of 8.3 years and M: F ratio 1.4:1. The pilocytic astrocytoma represented 64.7% of all astrocytic tumors. The second malignant tumor was embryonal tumors (medulloblastoma) and accounted for 18.3 % of CBL with male predominance. In conclusion, a single institute experience was reported revealing that primary CNS tumors were the commonest brain lesions in the pediatric age. Furthermore, in concurrence with the national and international experience, astrocytic tumors ranked as first primary CNS tumor of childhood age, followed by medulloblastoma.
[Hessa M. AlJhdali and Awatif A. Jamal. **Childhood Brain Lesions: 15 years Experience of King Abdulaziz University Hospital (1995-2010).** Life Sci J 2012;9(2):617-623]. (ISSN:1097-8135). http://www.lifesciencesite.com. 94

Keywords: Pediatric; brain; lesion; neoplastic; congenital malformation; inflammatory; medulloblastoma

1. Introduction

Pediatric age brain lesions can be of neoplastic and non-neoplastic nature and include benign or malignant, primary or secondary neoplasms, as well as congenital malformation, inflammatory or parasitic mass, different types of cysts and vascular lesions [1-2]. One of most concerning brain pathology in the childhood pediatric age group is brain tumor because children with CNS cancer do not share the favorable prognosis of those with many other common pediatric neoplasms [3]. Cancer of the brain and central nervous system comprise 17% of malignancies in children younger than 20 years of age and the leading cause of cancer death among children [4]. Malignant brain tumors are the second most common type of pediatric cancer after leukemia and it is the most common solid tumor [3-4]. The annual incidence rate of all primary non-malignant and malignant brain and central nervous system tumors is 16.5 cases per 1000,000 person/ year, and in pediatric age, the annual incidence rate for primary non–malignant and malignant brain and central nervous system tumors is 4.5 cases per 100,000 person/ years [5]. In the United state approximately 2200 children younger than the age of 20 are diagnosed with a brain tumor each year [3].

Brain tumor represents 22% of the total childhood cancers (< 15 years of age) in Europe, and account for 16% of total childhood cancer in Latin America, 4% in Africa and 19% in East Asia [6]. Studies from the Central and Eastern provinces of Saudi Arabia reported lower incidence of childhood primary CNS tumors. **Akhtar & Reyes** [7] showed that Lymphomas (Hodgkin's disease accounted for 34%, Non-Hodgkin's Lymphoma accounted for 32%) was the commonest tumors among the children under 14 years, leukemias accounted for 19.35% and brain tumors ranked third and accounted for 6.45% of pediatric age tumors. **Ibrahim** [8] documented a lower rate of CNS neoplasms in the Eastern province. The total cases of primary CNS tumors identified per annum were 43 cases, the incidence of primary CNS neoplasms was 3.1/100,000 of the total population and it was 2.9/100,000 in Saudis. Saudi Cancer Registry 2007 [4], reported that childhood cancers accounted for 7% of all cancers among Saudis and brain (CNS) cancer accounted for 11.3% of all childhood cancers and it is second cause of childhood cancer after Leukemia which accounted for 34.6% in Saudi children. The incidence of childhood primary CNS neoplasms in Saudi Arabia is far less than the

incidence reported in North America & Europe, but it is similar to that reported for Chinese and black Americans and it is less than the one reported by the Ashkenazi or Safari Jews [8].

Gurney *et al.* [3] reported that the most frequent encountered brain tumor is astrocytomas which accounted for 52% of childhood brain tumors, followed by cerebellar PNET (medulloblastoma) which accounted for 21%, ependymomas accounted for 9%, and other gliomas accounted for 15%.

Ansari & Al-Hilli [10] showed that the incidence of malignant brain and spinal cord neoplasms in Bahrain is very low and might be attributed to the small number of Bahraini population, inefficient registration of cancers, and the lack of routine hospital autopsies. Amongst the Bahraini population, astrocytomas were the most common tumor seen in children and comprised 25% of malignant primary CNS tumors. Medulloblastoma ranked as second malignant primary CNS tumor and accounted for 16.9% of all primary CNS neoplasms. Astrocytomas and medulloblastoma were the commonest primary malignant CNS neoplasms in both adults and children.

Jamjoom[1] revealed that neuroepihelial tumors were the most common intracranial neoplasm (39.7% of the total) and they constituted 73% of all brain tumors below the age of 15 years. **Memon *et al.*** [11] & **Zakrzewski *et al.*** [12] supported the fact that astrocytoma is the most frequent childhood tumor. However, institutional based studies carried in Pakistan by **Ahmed *et al.*** [13] documented predominance of medulloblastoma and paucity of astrocytoma. Furthermore, **Nasir *et al.*** [14] study reported that medulloblastoms did account for 33.3% and astrocytoma accounted for 24.7% of all primary brain tumors among children.

Cerebral neoplasms are heterogeneous tumors in regard to histology and clinical course; there are several classification systems to describe CNS tumors. The World Health Organization Classification System [15] and the American Collage of Pathologists update [16] were used in the current study to classify CNS neoplasms.

The objective of the current study to report all Childhood brain lesions diagnosed at King Abdulaziz University Hospital over a period of 15years (from 1995 to 2010), including the frequency, the histo-pathological entities encountered, the age distribution and the gender of the patients. Furthermore, it compared the study findings with national and international experience.

2. Materials and Methods

A retrospective study performed using a computerized search of the archives of Histopathology Department at King Abdulaziz University Hospital in Jeddah from 1995 tell 2010 to retrieve all the brain cases inclusive of all brain regions. The data was collected using appropriate morphological SNOMED codes (Systematized Nomenclature of Medicine) obtaining the following information, receiving date of the specimen, Hospital identification number, demographic information (age & gender), clinical diagnosis, topography and morphology information. Data double checked, exported to Microsoft Excel program and SPSS program (version14) for analysis. Out of the 283 cases of brain lesions retrieved from the archives between 1995- 2010, Seventy one cases (71) represented the study group of childhood brain lesions, the cut off age range used to represent the pediatric age group in the present study is from 0 day to 18 years.

The pathological reports and available H&E sections as well as the available performed immune-histochemical stained sections, were collected and revised by the pathologist. Detailed radiological imaging as MRI images or both CT and MRI imaging studies information before and after treatment were available from the Radiology Department for the majority of the cases. Detailed Clinical data and follow-up data of the patients were beyond the scope of the study, except for the concise and brief information attached to the pathology request.

3. Results

The current retrospective study is based on histo-pathological review, associated with radiological correlation, of total brain lesions received during 1995 – 2010 at the Department of Histopathology at King Abdulaziz University (KAUH).

A total of 283 brain surgical cases were received and were 152 (53.7%) male cases and 131 (46.3%) female cases. M: F ratio was 1.2:1 and the age ranged between 0day-99 years (mean age 33.5 years). The cases were divided into two age groups, Adult brain lesions and Childhood brain lesions (Table 1).

71 cases out of 283 cases of total brain lesions were childhood brain lesions and accounted for 25.1% of the total brain lesions with mean age of 6.9 years and M: F ratio of 1.6:1. The frequency of various histological childhood brain lesions in the study were: congenital malformations accounted for 23.9%, infection and inflammatory lesions accounted 12.7%, benign lesions accounted for 4.2% and primary brain tumors accounted for 59. 2%. The total primary brain tumors were neuroepithelial tumors accounted for 25.4%, and non-neuroepithelial tumors accounted for 33.7% (Figure 1). The most common childhood brain tumors diagnosed were the neuroepithelial tumors 18 cases accounted for 25.4% and 13 cases of embryonal tumors and accounted for 18.3% of total brain lesions. Mesenchymal and meningeal tumors were 5 cases and accounted for 7% of benign tumors and sellar region tumors and germ cell tumors each accounted for 4.2% (Figure 1). Embryonal tumors and tumors of the

mesenchymal and meninges, showed male predominance.

Table 1. The Percent of Total Childhood Brain Lesions out of Total Brain Lesions (1995-2010) at KAUH.

Total Brain Lesions= 283 case	Age Range	M:F Ratio	% of Total Brain Lesions-283
Adult Brain Lesions= 212 cases	**19-99 yrs (Mean= 45.3yrs)**	**1.1 M: 1 F**	**74.9%**
Childhood Brain Lesions= 71 cases	**0day-18yrs (Mean= 6.97yrs)**	**1.6 M: 1 F**	**25,1%**

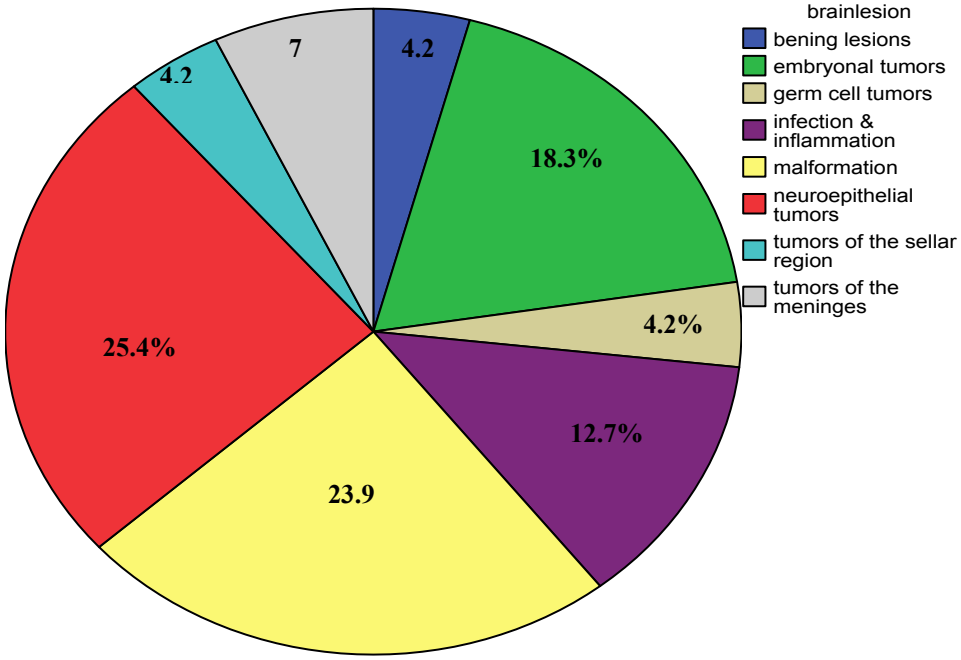

Figure 1. Frequency of the Various Histological Childhood Brain Lesions (1995-2010) at KAUH

The Glial astrocytic tumor (94.4%) accounted for the majority of the neuroepithelial tumors, 17 cases were diagnosed with age ranging between 1- 18 years (mean age 7.9 years) and M: F ratio of 1.4: 1. All grades of Glial astrocytic tumors according to WHO 2007 were identified in this study [15-16]. The pilocytic astrocytoma (Grade I) represented 64.7% of all astrocytic tumors with mean age of 8 years old and M: F ratio of 1.2:1 (Table 2). Clinically these neoplasms occurred mainly in the posterior fossa or cerebellum and histologically composed of fibrillary glial tissue with highly vascularized tumor exhibiting compact and loose areas. The compact areas show bipolar piloid cells with long-hair like processes associated with Rosenthal fibers. Microcytic areas and eosinphilic granular bodies admixed with protoplasmic astrocytes represented the loss textured areas. The Grade II neoplasms accounted for 17.6% with age distribution between 5-12 years old. These neoplasms occurred in various lobes mainly frontal and temporal and showed the classical diffuse neoplastic astrocytic cells proliferation in a fibrillary background with the cells exhibiting mild pleomorphism and hyperchromasia. Grade III the anaplastic glioma occurred in a 10 years old child and accounted for 5.9%, histologically the neoplasm expressed higher morphological atypia and cellularity. Grade IV encountered in 2 cases histologically showed high grade cytological atypia with bizarre nuclei, frequent abnormal mitosis, variation of appearance from one filed to another associated with the classical necrosis and increased glomoriloed blood vessels proliferation.

Congenital malformations was the second encountered brain lesions (10 encephalocele, 4 meningocele and 3 myelomeningocele); this group represented the youngest age group (mean age 2.8 years). The next category was infection and inflammation forming inflammatory masses within the brain and prompting a biopsy for histo-pathological diagnosis and accounted for 12.7% of all brain lesions (4 cases were abscesses, 2 granulation tissue, 1 aspergillosis, 1 edema with necrosis, 1 chronic non-specific inflammation). Almost equal M: F ratio was found and the mean age was 11.2 years. Embryonal tumors were third in line (12 cases medulloblastoma and 1 case neuroblastoma) and observed in males only with mean age of 5.3 years; no female cases identified in the study. The available pathological- radiological

correlations of the medulloblastoma cases were obtained. Data about the tumor site, tumor size, the presence of metastasis or residual tumor after treatment was collected. Majority of the cases were reported as classic medulloblastoma (83.3%) displaying anaplastic features, including increased nuclear size, marked cytological pleomorphism, numerous mitoses and pseudo-rossites. In five cases the tumor was located in the midline of the cerebellum, one case showed evidence of dorsolumbar spine metastasis, one presented with residual tumor after surgical resection and two of the patients deceased after diagnosis (Table 3).

Table 2. Percentages of Various Grads of Neuroepithelial Lesions and Age Range

Neuroepithelial Tumors= 18 cases	Age Range
Astrocytic tumors = 17 (94.4%)	**(Mean= 7.9yrs)**
Grade I = 11 cases (64.7%)	**1 – 18 yrs**
Grade II = 3 cases (17.6%)	**5 – 12 yrs**
Grade III = 1 case (5.9%)	**10 yrs**
Grade IV = 2 cases (11.8%)	**9 – 10 yrs**
Ependymal Tumors = 1 (5.6%)	**1yrs**

Table 3. Embryonal Tumors at KAUH (1995-2010).

Medulloblastoma (MB)= 12 cases	Age Range	Size Range of The Tumor	Site	Metastasis
Classic MB = 10 **Desmoplastic MB = 1** **Neuroblastic MB = 1**	**2-10 yrs** **Mean= 5.7yrs**	**3-6.6 cm** **Mean= 4.3cm**	**Midline= 5** **RT cerebellum= 4** **Disseminated=1** **Not available = 2**	**1 (8.3%)** **Dorsal lumbar spine**

There were 5 cases of meningeal/ mesenchymal tumors according to the WHO classification (4 mesenchymal tumors and one meningioma). All were diagnosed in males with mean age of 10.2 years. The meningioma case was anaplastic type grade III and occurred in a 15 years old male. The other mesenchymal tumors included 2 haemangiomas, one lipoma and one myxoma. The tumors identified in the sellar region were 3 cases, 1 case was craniophrangioma and two were pituitary adenomas. The germ cell tumors were also 3 cases (2 mature teratoma and one mixed germ cell tumor) with mean age of 5.6 years and M: F ratio of 1: 2. The last category comprised 3 cases of benign lesions including two vascular lesions and one benign meningoepithelial cyst (Table 4).

4. Discussion

In Saudi Arabia the experience of childhood brain lesions in general and brain tumors in particular is not extensively documented. Unfortunately many of the epidemiological studies that focused on brain tumors are confounded by selection bias conferred by sole reliance on tertiary referral centers and tertiary referral hospitals in the various regions of the kingdom. No integrated unified Brain Cancer Registry is instituted. However, the small number of the reported studies attempted to give mainly an estimate of the frequency and incidence of brain tumors in this pediatric age group, the frequent histological type, the age range distribution and gender.

Brain lesions in general can be caused by injury, infectious diseases, exposure to certain chemicals or ionizing radiation, problems with the immune system, and other factors [3]. Although different environmental exposure was proposed to be related to the development of childhood brain tumors; many investigators claim that childhood brain tumors reflect the inherent risk associated with the complex process of normal development rather than a response to an external toxic insult [4-17].

The current study over a period of 15 years estimated the frequency of brain lesions and highlighted the institute experience with the pediatric age group brain lesions (non-neoplastic and neoplastic lesions). 40.8% were non-neoplastic and 59.2% were neoplastic lesions. Congenital malformations were the commonest non-neoplastic brain lesions while astrocytoma was the most frequent tumor in the pediatric age group.

Only few studies included neoplastic and non-neoplastic brain lesions, **Jamjoom** [1] conducted a study on 212 brain cases diagnosed at King Khalid University Hospital in Riyadh over a period of 5 years and reported that the non-neoplastic brain lesions represented only 13% of the total brain lesions and that neoplastic brain lesions represented 87% of all brain lesions. Abscess, granulomas, gliosis and mucocele

were among the non-neoplastic brain lesions and represented 50%, 42.8%, 3.6% and 3.6% respectively of the total intracranial space occupying non-neoplastic lesions. Neuroepithelial tumors ranked first neoplastic lesions and comprised 39.7% of the total intracranial neoplasms and 73% of all brain tumors seen below the age of 15 years [1].

Table 4. Childhood Brain Lesions at KAUH (1995-2010).

Brain Lesions (Frequencies)	Age Range	Gender Ratio
Congenital Malformations = 17 cases **Encephalocele = 10** **Meningocele = 4** **Meningomyelocele = 3**	**0 day – 15 yrs (Mean= 2.8yrs)**	**1 M : 1.1 F**
Infection and Inflammation = 9 cases **Abscess = 4** **Granulation tissue = 2** **Aspergillosis = 1** **Edema with Necrosis = 1** **Chronic Non-specific Inflammation = 1**	**1-18 yrs (Mean= 11.2yrs)**	**1 M : 1.3 F**
Benign Lesions = 3 cases **Vascular Lesion = 2** **Benign Meningioepithelial Cyst = 1**	**3-16 yrs (Mean= 7.7yrs)**	**1 M : 2 F**
Neuroepithelial Tumors = 18 cases	**1-18 yrs (Mean= 7.9yrs)**	**1.6 M : 1 F**
Non- Neuroepithelial Tumors = 24 cases **Embryonal Tumors = 13** **Tumors of the Mesenchem & Meninges = 5** **Tumors of the Sellar Region = 3** **Germ Cell Tumors = 3**	**1 day-18yrs (Mean= 7.5yrs)**	**5 M: 1 F**

Table 5. Morphological Distribution of Childhood Brain Tumors, Comparison of Current Study and other Published Studies

References	Location	Period of Study	Total (n) of all tumor cases	Most common Pediatric Tumor
Current study	Saudi Arabia, Jeddah	1995 – 2010	42	Astrocytic tumors 40.5%
Rickert *et al.*, 2001	Germany	2001	340	Astrocytic tumors 37.6%
Zakrzewski *et al.*, 2003	Poland	1990 – 2003	216	Astrocytic tumors 41.5%
Rosemberg *et al.*, 2005	Brazilian	1974 – 2003	1195	Astrocytic tumors 32%
Ahmad *et al.*, 2007	Karachi, Pakistan	1989 – 1998	81	Astrocytic tumors 34.6%
Nasir *et al.*, 2010	Islamabad, Pakistan	Jan1998 – July2010	231	Medulloblastoma 33.3%
Saavedra *et al.*, 2011	Puerto Rico	2002 – 2007	136	Astrocytic tumors 31%

The current study showed higher percentage of non-neoplastic lesion in comparison with **Jamjoom** [1] experience, this might be attributed to the study design, number of cases, and the study period, furthermore, it might reflect advancing in the imaging techniques and diagnostic expertise as well as treatment modalities. However, the study consensus with the generated experience from the various regions of the kingdom, and it demonstrated that neuroepithelial tumors, mainly glial tumors, are the most frequent brain tumors encountered in the pediatric age group and accounted for 25.3 % of all childhood brain lesions with slightly higher frequency in male and M: F ratio of 1.4:1. Pilocytic astrocytoma was the leading tumor in this age group in the study and represented 64.7% of all astrocytic tumors with M: F ratio of 1.2:1. The second most frequent tumor was embryonal tumor (medulloblastoma) which accounted for 18.3 % and showed male predominance. The current study findings compatible with **Gurney *et al.*** [3], were they reported male predominance of the childhood brain tumors. However, many national and international studies showed male predominance of both astrocytic and medulloblastoma tumors [12, 13, 18, 19].

The literature displayed a dispute between astrocytoma and medulloblastoma tumors as which compete for the highest frequency. The current study

confirm the previous experience which revealed preponderance of astrocytoma as was reported by **Richert *et al.*** [18] were he reported that astrocytoma comprising 37.6%, followed by medulloblastoma 17.7%. Similar reports by **Zakrzewski *et al.*** [12], **Rosemberg *et al.*** [19], **Memon *et al.*** [11], and **Ahmad *et al.*** [13] were their experience revealed the prevalence of astrocytic tumors as the leading childhood brain tumor followed by medulloblastoma. Furthermore, they reported that Pilocytic astrocytomas are the most frequent grade encountered among the Glial tumors confirming the finding of the current study. Furthermore, **Ansari & Al-Hilli** [10] observed that among the Bahraini population, astrocytic tumors are common in children and representing 25% of primary CNS tumors but with predominance of diffuse fibrillary astrocytoma. Medulloblastoma ranked as second malignant primary CNS tumor and accounted for 16.9% of all primary CNS neoplasms.

In contrast to the current study finding, Saudi Cancer Registry had meduloblastoma as the first leading childhood brain tumor in their series [9, 14]. **Nasir *et al.*** [14] also reported medulloblastoma to be the first ranking children brain tumors under the age of 14 years with a mean age of 6.2 years and they accounted for 33.3% of their cases. Astrocytoma was the second most dominant type accounted for 24.7%, with a mean age of 6.7 years. This discrepancy in findings between studies could be attributed to variation in the ethnicity, race, and selection bias and to the size of the study population. Furthermore, it might be related to the selected cutoff age range of childhood age, which varies between studies especially if we consider the various peak of occurrence of some brain tumors.

Classical type medulloblastoma was the dominant type in our study and other studies with mean age of occurrence 5.7 years [14, 20, 21]. **Rodriguez *et al.*** [22] reported that 73% of the medulloblastoma cases were classical type, 45% occur in cerebellar hemisphere.

The number of cases presented in the current study is smaller in comparison to the reported national and international studies [12, 13, 14, 19, 23] (Table 5). This might be attributed to ineffective case registration, or difficulty in access the established health care system like the University center, or it may be due to limitation of the diagnostic facilities (such as radio-imaging techniques or histopathological diagnostic experts) in early years. Another plausible explanation could be the low ethnic- racial predisposition in the Eastern region of the Kingdome, or a lower prevalence of the risk factors resulting in lower brain lesions / tumors frequency/incidence in the Eastern region. This latter proposal is detected in South Africa population where the incidence of intracranial neoplasm's in whites was higher than in blacks [4].

5. Conclusion

This is single institute study presenting the King Abdulaziz University Hospital experience with childhood brain lesions over a period of 15 years. The results were consistent with national and international experience regarding the childhood neoplastic and non-neoplastic brain lesions. The findings call for a large scale nationwide study to determine the incidence and prevalence of the childhood brain tumors and provide better categorization of this important pediatric pathology among Saudi population.

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4/4/2012