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MEDULLOBLASTOMA: RECAPITULATE DIVERGENT TUMORAL CELLS DYNASTIES

Medical Science

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ABSTRACT

INTRODUCTION: Medulloblastoma is one of the most frequent, violent, invasive, malignant embryonal tumor of the posterior fossa with a partisan demonstration in children. Of 2200 children diagnosed with a brain tumor in the United States, medulloblastoma accounts for 22% of all childhood primary tumors

OBJECTIVES: Current study aims to use a retrospectively collected data registry of the surgically treated cases of medulloblastoma to clarify the relative frequencies in our setup over a period of 15-years.

METHODS: This retrospective study was conducted under approval by the institutional ethical committee. Institutional patient database of 82-patients who underwent surgical intervention by the Department of Neurosurgery in a single referral center – King Hussein medical center-over a fifteen-year period from January 2002 to January 2017 scrutinized. The clinical diagnosis was confirmed by radiological studies and histopathological reports in all patients. Patients with age ranging from neonate to 18 years were included in the study.

RESULTS: Of the total population consisted of 82-patients, 34 were females and 48 were, 17.1% of medulloblastomas were in children 1-4 years, 39.02% in the 5-9 years, 35.4 % was in 10-14 age group, while 8.53% in older children (14–18 years). Headache and recurrent vomiting were the most common presenting symptoms. Cerebellar ataxic gait was the most common manner of presentation in children younger than 14 years. Drop Mets were present in approximately 29.3% of patients at time of diagnosis. Dilated ventricular system revealed in 57-cases at the time of diagnosis. Symptomatic hydrocephalus was evident in 29-cases as primary presentation, Pre-operative ventriculo-peritoneal shunt inserted in 18-cases, while 22-cases underwent ETV, the reset underwent primary tumor resection. Post tumor resection 16-cases needed shunt procedures. All patients above 4-year old were sent to radiotherapy. Cerebellar mutism syndrome observed in 18- patients. In total, eleven patients underwent a second operation-resection.

CONCLUSION: Medulloblastoma considered one of the most devastating illnesses, predominantly showing up in children with peak incidence in the first decade, clinical presentation is insidious. Management of medulloblastoma include surgery, adjuvant radiation therapy and/ or chemotherapy. Recent advances in imaging modalities and treatment options and molecular fields, have conveyed about a great improvement in survival in these patients, with recurrence rates relatively low due to a feasible gross total excision and relatively longer survival rate.

KEYWORDS

Posterior fossa; medulloblastoma; mutism; drop-metastasis; embryonal tumor

INTRODUCTION:

Medulloblastoma is one of the most frequent, devastating, violent, invasive, malignant embryonal tumor of the posterior fossa with a partisan demonstration in children. It arises in the cerebellum with an incidence of ~0.74 per 100,000 person-years [1, 2]. Medulloblastoma is the most frequently reported malignant pediatric tumor in the central nervous system (CNS), accounting for nearly 22% of all childhood brain cancers and ~40% of all childhood tumors in the posterior fossa [3-5]. Previous studies have identified differences in the cell of origin, tumor cell differentiation, and pathological features, categorizing Medulloblastoma as embryonal neuroepithelial tumor of the central nervous system, with several recognized morphological variants: classic medulloblastoma, large cell/anaplastic medulloblastoma, desmoplastic/nodular medulloblastoma, and medulloblastoma with extensive nodularity. Recent advances in transcriptome and methylome profiling of these tumors led to a molecular classification that includes 4 major genetically defined groups [6, 7].

New progresses in imaging and treatment options (particularly surgery and radiotherapy) have conveyed about a great improvement in survival in these patients over the past few decades [8- 12]. Large multi-institutional reports illustrating the epidemiology and morbidity of Medulloblastoma surgery are lacking Current study aims to use a retrospectively collected data registry of the surgically treated cases of the Medulloblastoma to delineate the epidemiological features in our setup over a period of 15-years. Special emphasis devoted to analyze the incidence, available treatment modalities and impact in such cases.

METHODS:

This retrospective study was conducted under approval by the institutional ethical committee. Institutional patient database of 82-patients who underwent surgical intervention by the Department of Neurosurgery in a single referral center – King Hussein medical center-over a fifteen-year period from January 2002 to January 2017 scrutinized. The clinical diagnosis was confirmed by radiological studies (CT scan, MRI…) and histopathological reports in all patients. Patients with age ranging from neonate to 18 years were included in the study.

RESULTS:

Of the total population consisted of 82-patients, 34 were females and 48 were males giving a male: female of 1.4:1 in our series, 17.1% of medulloblastomas were in children 1-4 years, 39.02% in the 5-9 years, 35.4 % was in 10-14 age group, while 8.53% in older children (14–18 years) [Figure. 1]. Headache and recurrent early morning vomiting were the most common presenting symptoms with duration of symptoms ranged between 1-week and 21-weeks in extreme cases.

Fig. I: Diagram Showing The Gender Distribution Among The Different Age Groups Allocated.

Cerebellar ataxic gait was the most common manner of presentation in children younger than 14 years. All patients underwent imaging protocol of the entire neuraxis, due to medulloblastoma's tendency for spread along the cerebrospinal fluid (CSF) pathways with resultant drop metastases and leptomeningeal disease. It is our protocol to do brain and whole spine MRI with and without contrast. Drop Mets were present in approximately 29.3% of patients at time of diagnosis. Dilated ventricular system revealed in 57-cases at the time of diagnosis. Symptomatic hydrocephalus was evident in 29-cases as primary presentation, Pre-operative ventriculo-peritoneal shunt inserted in 18-cases, especially before we introduced the cranial endoscope to perform endoscopic third ventriculostomy [13]. While 22-cases underwent ETV, the reset underwent direct tumor resection. Post tumor resection 16-cases needed shunt procedures. All patients above 4-year old were sent to radiotherapy, while patents below 4-year were sent for chemotherapy. Cerebellar mutism syndrome observed in 18- patients, and was in sever, completely- irreversible form in 4-cases. In total, eleven patients underwent a second operation-resection during the follow-up within 1-38 months. The verdict for re-do surgery was based on clinical condition and/or progression on radiology images (MRI-based indications of increase tumor residual.

DISCUSSION:

Researches nowadays are committed to elicit more profound information about medulloblastoma, ways to prevent it, optimal treatment, and how to provide the best care to children diagnosed with this disease. Results from these studies may help develop specific treatments for each type of medulloblastoma.

Based on histological match between medulloblastomas and other small round blue cell tumors arising in areas outside of the posterior fossa, it was proposed that these tumors be classified together under the egis group of primitive neuroectodermal tumors (PNETs) [13, 14]. However, the most recent WHO classification, distinguishes medulloblastoma and its subtypes from other CNS PNETs, pineoblastomas, and atypical teratoid/rhabdoid tumors [14-16]. Medulloblastomas represent 61.9% of all embryonal tumors, followed by atypical teratoid/rhabdoid tumors (ATRT) (15.0%), primitive neuroectodermal tumors (PNET) (14.9%) [1].

Rates of medulloblastoma diverse in many sources, some have stated that medulloblastoma is the most common malignant brain tumor in children, however, the most contemporary data illustrate that high-grade gliomas, as a group, are slightly more prevalent. Medulloblastoma represents 9.2 percent of pediatric brain tumors in children aged 0-14 years [1, 14, 17-19]. Medulloblastoma is slightly more predominant in males, with a male to female incidence rate ratio of 0.63 [20]. In our review, 34 were females and 48 were males giving a male: female of 1.4:1.

Clinically, medulloblastoma symptoms generally evolve over a period of weeks to months. A combination of signs and symptoms of cerebellar dysfunction and increased intracranial pressure (ICP) are frequently encountered. Signs of cerebellar involvement are more likely to result in truncal ataxia. Additionally, cranial nerve involvement may be present either as a result of direct involvement of these nerves or as a consequence of increased ICP. In our review outcomes were in line with the stated reports, nevertheless, in cases where drop-Mets are present, symptoms related to the location of metastatic involvement may also be observed [Figure. 2].

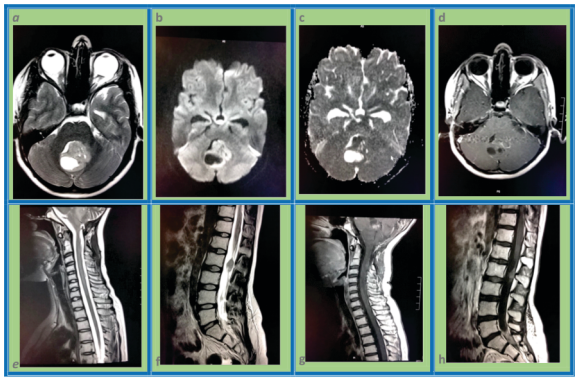

Fig. I [a-h]: Radiological images of a 15-year old boy, presented with ataxia, headache, vomiting and low back pain : a)

Axial T2WI shows a hyper intense lobulated fourth ventricular tumor with internal variable sizes cystic components expanding the fourth ventricle and abutting the dorsal brain stem with mild vasogenic edema, b, c) Diffusion and ADC map: the lesion appears bright in diffusion & dark in ADC map with low value indicating high cellularity, d) Post contrast TIWI: the lesion exhibits mild heterogeneous spotted enhancement of the non-cystic component, e) Sagittal T2WI of the cervical demonstrates irregular surface of the cervical cord with multilevel surface nodularity along with intramedullary T2 iso to hyper intense lesions, f) Sagittal T2WI of the lumber spine demonstrates multiple intradural variable sizes lesions most marked opposite L2 and S1 which appears isointense in T2, along with surface nodularity and intrinsic cord lesion at the conus medullaris, g) Post contrast TIWI: the lesion exhibits mild heterogenous spotted enhancement of the non-cystic component., h) Sagittal T1 post contrast of the lumbar spine shows diffuse nodular leptomeningeal enhancement along with multiple intramedullary and intradural enhancing deposits which is consistent with drop metastasis and leptomeningeal spread.

Radiological investigations include; computed tomography (CT), usually medulloblastoma demonstrates as a hyper dense lesion which arise from the vermis with cystic formation or necrosis. Calcification detected in 10-20% [Figure.3]. Magnetic resonance imaging (MRI) with different sequences is the gold standard. On MRI, medulloblastomas appear hypo intense on T1-weighted with heterogeneous vivid gadolinium enhancement in 90%, while, on T2-weighted imaging they are generally iso- to hyper intense and commonly appear heterogeneous due to cystic formation, calcification and necrosis. Diffusion-weighted and ADC mapping imaging shows high signal in DWI with low signal in ADC map indicating restricted diffusion which is typical for medulloblastoma due to high cellularity. Medulloblastomas arise from the cerebellar vermis and tend to protrude into the fourth ventricle, even though the site of origin in adults is more frequently the cerebellar hemispheres. Effacement of the fourth ventricle and ventricular dilatation secondary to obstructive hydrocephalus are often seen [Figure. 4].

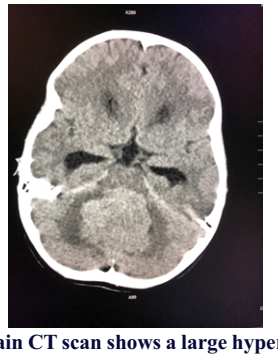

Fig. III: Axial brain CT scan shows a large hyper dense soft tissue mas lesion with lobulated margins centered in the 4th ventricle, with no internal calcifications or hemorrhage.

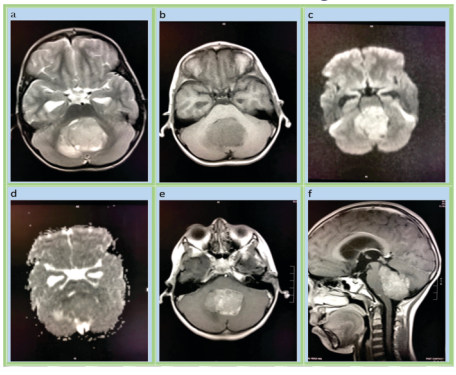

Fig. VI [a-f]: Radiological images of a 15-year old boy, presented with ataxia, headache, vomiting and low back pain :a)

Axial T2WI: the lesion appears hyper intense contains few small cystic components, compressing the dorsal brain stem resulting in obstructive hydrocephalus in the lateral ventricle (temporal horns) surrounded by mild perilesional edema, no evidence of invasion into

the brain stem or cerebellar hemispheres, b) Axial T1WI: lesion appears hypo intense, c & d) Diffusion & ADC mapping study demonstrate high DWI signal with low ADC value and signal indicating restricted diffusion consistent with the high cellularity of the tumor, e & f) Axial and sagittal T1 post contrast: demonstrates marked heterogenous enhancement.

Current treatment strategies tailor treatment endorsements based on the pathophysiology of medulloblastoma, clinical condition at presentation and age. Nevertheless, recent technological and research advancements has made the surgery of medulloblastoma safer. The treatments modalities available are used in combination. The guiding principles for the neurosurgeon remains safe maximum resection, as there is no rationalization for removal of small tumor from critical locations causing major deficit. Our protocol for management is: if patient received with hydrocephalus and neurological manifestations, the first step is to divert the CSF either by ETV or shunt placement. Once the patient stabilized we perform brain and whole spine MRI pre and post contrast aiming to assess tumor extent and dissemination. Posterior midline cranioectomy is our standard approach. Staging is dependent upon extent of resection, evidence of tumor spread, and CSF cytology so we perform early post-operative radiological surveillance [13, 21].

Post-operative complications vary encompassing: hydrocephalus, hematoma, mutism and aseptic meningitis. Our review showed symptomatic Hydrocephalus in 29-cases as primary presentation, dilated ventricular system in 57-cases at the time of diagnosis. Pre-operative ventriculo-peritoneal shunt inserted in 13-cases. While 22-cases underwent ETV, the reset underwent direct tumor resection. Post tumor resection 16-cases needed shunt procedures. All patients above 4-year old were sent to radiotherapy, while patents below 4-year were sent for chemotherapy.

Cerebellar mutism syndrome observed in 18- patients, and was in sever, completely- irreversible form in 4-cases. In total, eleven patients underwent a second operation-resection during the follow-up within 1-38 months.

Treatment of medulloblastoma has evolved impressively over the foregoing decades, Medulobalstomas in recent research found to be highly heterogeneous and have diverse genetic characters, with differential microRNA expression profiles and variable prognoses [22, 23]. Novel therapeutic options which may be less lethal than current standard treatments are under consideration depending on clinical elements such as age, magnitude of resection, and presence of metastases. Molecular biology is launched to improve upon clinical prognostication and may soon provide the means to accurately envisage response to therapy. However, further studies are justified to be done to effect reliable cures while reducing long-term sequelae of therapy.

CONCLUSION:

Medulloblastoma considered one of the most devastating forms of human illnesses, predominantly showing up in children with peak incidence in the first decade, clinical presentation is insidious, with coexistent clinical manifestations of increased intracranial pressure and cerebellar involvement. Management of medulloblastoma include surgery, adjuvant radiation therapy and/ or chemotherapy. Recent advances in imaging modalities, treatment options and molecular fields, have conveyed about a great improvement in survival in these patients, with recurrence rates very low due to a feasible gross total excision and relatively longer survival rate.

LIMITATIONS

This study has several limitations. First, a quantitative analysis couldn't be established due to great heterogeneity in the included treatment policies, different surgeons of different levels.

FUTURE DIRECTIONS

We are planning more focused reviews on clinical forms and adjuvant therapies. The histopathological diagnostic approach for medulloblastoma subtypes which is dramatically changing.

CONFLICT OF INTEREST STATEMENT: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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