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FACULTÉ DE MÉDECINE ET DE PHARMACIE

MEDULLOBLASTOMA : A 3 YEAR EXPERIENCE AT THE NEUROSURGICAL DEPARTMENT OF THE UNIVERSITY TEACHING HOSPITAL OF FEZ

Mémoire présenté par

Docteur MFOUAPON EWANE Herve Blaise

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Sommaire

DEDICATION

This work is dedicated to my twin sister of late NZIE EWANE Juliette Christelle you passed away so early may your soul rest in perfect peace. You went ahead we shall follow you. I miss you so much.

To my tutors Professors CHAOUI, CHAKOUR, BENZAGMOUT, AGGOURI, LAKHDAR

Thanks for having receiving me, thanks for your mentorship for your patience and for having tought me. What I learnt from you will be a lasting experience

To my Father, ETAME MASSOMA thanks for your support. You have always been the perfect dad. I dedicate this work to you

To my mum, YAKUE Regine, a mother remains a mother…. Words are insufficient to express my feelings for you

My wife Marianne and our two daughters Aude and Orchidee ; you are the reason of me thriving daily to be better

MY brothers Lawson, Elvis, Lessly, Frank, Yves and Ludovic. Despite the distance I always think of you guys

My family and friends atlarge thanks for the support.

ABBREVIATIONS

Cytomegalovirus	: CMV
CT	: computed tomography
Familial adenomatous polyposis	: FAP
fibrillary acidic protein	: GFAP
Gross total resection	: GTR
Large cell anaplastic	: LCA
Medulloblastoma	: MB
MR	: magnetic resonance
Near total resection	: NTR
Desmoplastic/nodular medulloblastomas	: MBEN
Nevoid basal cell carcinoma syndrome	: NBCCS
Primitive Neuro Ectodermal Tumors	: PNETs
Radiation therapy	: Xrt
World Health Organisation	: WHO

INTRODUCTION

I. INTRODUCTION

Medulloblastoma (MB) was first reported by Bailey and Cushiing in 1925 [1]. It is an aggresive tumor of the posterior fossa that is thought to originate from the neural stem cells precursors in the granular cell layer of the cerebellum [2]. It is the most common malignant primary brain tumor in childhood and is less present in adults.

With a near 100% mortality rate initially, it represented a neurosurgeon's nightmare— an aggressive neoplasm located in one of the most challenging sites in a young child, who is almost certain to die from the disease within a matter of months or less. From these stark beginnings, substantial improvement in survival has been made because of a combination of several factors. Over the past 20 years, clinical variables have been used to stratify patients with medulloblastoma into average or standard risk and high risk[3]. Current risk stratification tools have been in place for decades and are based on clinical features including age at diagnosis, extent of surgical resection, metastatic status, and in some cases histological features [4].

Nowadays, overall survival rates for patients with medulloblastoma has improved reaching 70-80% using treatment protocols that include a combination of surgery, cranio-spinal radiotherapy and chemotherapy [5]. Although conventional therapies cure a large proportion of patients with medulloblastoma, the majority of survivors suffer from long-term side effects including developmental, neurological, neuroendocrine, and psychosocial deficits [6].

The World Health Organisation (WHO) classification system 2007 for medulloblastoma uses histology to classify medulloblastomas into three classic subtypes. Molecular biological studies have created a new understanding of

medulloblastomas, revealing key cell signaling pathways that promote tumor growth. Biological markers that serve as prognostic indicators and which will provide therapeutic targets in the very near future **[7].** Through an improved understanding of the molecular and genetic basis of medulloblastoma, it is anticipated that patients will be stratified and treated according to the biological make up of their disease in the future, leading to improved patient outcomes with reduced sequela.

Previous studies of medulloblastoma therapy have demonstrated the importance of surgical resection and postoperative radiotherapy. Chemotherapy is performed supportively in children with the purpose of reducing the radiation dose and postponing radiotherapy until the patient is at least 3 years of age. However, the role of chemotherapy in treatment of medulloblastoma in adults is also important.

Although many potential risk factors for brain and head and neck cancers have been identified including smoking and chewing tobacco, alcohol consumption, poor diet combined with hypoduynamic lifestyle, acid reflux disease, haemopoetic stem cell transplantation, ionising radiation, electromagnetic fields and exposure to carcinogenic chemicals, various pathogenic infections also constitute an under-appreciated but significant risk **[8].** The human cytomegalovirus (CMV) has been detected in human medulloblastoma lines. This has been described by some authors to play a role of oncomodulator in the development of medulloblastomas **[9].** However the oncogenic role of CMV in medulloblastoma is still an ongoing controversy in the literature.

We will make a literature review concerning the pathology and the current trends of management and the role of CMV in medulloblastoma.

As well we will present our day to day experience on the management of medulloblastoma in our neurosurgical department but also in association with the

molecular biology department, our results on the association between medulloblastoma and CMV.

1. HISTORICAL BACKGROUND

Medulloblastoma was first reported in 1925 by Bailey and Cushing **[1]** who described 25 patients with densely cellular brain tumors of the posterior fossa that were fatal if radiation therapy (XRT) was not administered after surgery **[10].** Medulloblastoma was named after a still unidentified ''indifferent'' cell thought to be a precursor for both glial and neurons **[11].** In 1973, Hart and Earle **[12**], described a series of mostly adult patients who had small, round, blue cell tumors of the supratentorial fossa that did not fit into the current classification; they were called primitive neuroectodermal tumors (PNETs). This controversy in nosology was later extended by the combining of the histopathologically similar supratentorial PNETs with MB into the revised World Health Organization childhood brain tumor classification of all intracranial childhood embryonal brain tumors. On the basis of that World Health Organization revision, the term posterior fossa PNET was formally introduced, although MB has continued in use. In the early 1980's, based on histological similarity 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 umbrella group of primitive neuroectodermal tumors (PNETs).

Five-year survival rates of 50% to 80% have been reported with different treatment approaches over the past 25 years after the introduction of craniospinal radiotherapy with local boost and, later, chemotherapy **[13].** Prospective clinical trials by the Children's Cancer Group (CCG; CCG-942) and the International Society for Pediatric Oncology (SIOP; SIOP I) proposed vincristine (VCR), lomustine (CCNU), and prednisone (VCP) chemotherapy in addition to XRT could improve survival in higher-stage patients **[14].**

2. EPIDEMIOLOGY

Medulloblastoma is the most common malignant primary brain tumor in children with an estimated incidence of 0.5/100.000 [15] as it accounts for 20% of all tumors before 18 years and a peak incidence beteween the ages of 3-4 years old [16], in contrast to adults where it represents a rare tumor in adults and comprises less than 1% of adult primary brain tumor [17]. The annual incidence in the adult population is 1 in 2-20 million [18]. The incidence of MB is higher in males and higherer in arly childhood, with almost 50 percent (%) occuring before the age of 5Fewer than 5% of cases are associated with the hereditary cancer predisposition syndromes familial adenomatous polyposis (FAP), historically known as Turcot syndrome, or nevoid basal cell carcinoma syndrome (NBCCS), also called Gorlin syndrome. Two year overall survival ranges for young children with medulloblastoma range from 46 to 70% and 5 year overall survival ranges from 13 to 60% [19].

3. PATHOLOGY AND CLASSIFICATION .

3.1. HISTOLOGY.

The 2007 WHO classification system recognizes several histopathologic variants of medulloblastoma, all of which are categorized as grade IV neoplasms within the broader grouping of embryonal neuroepithelial tumors. Four histological variants are known ;

3.2. Classic medulloblastoma.

They represent the most common histological subtype with 66% **[20],** and is composed of sheets of densely packed small round blue cells (basophilic) with a high nuclear to cytoplasmic ratio, mitotic and apoptotic activity, and usually occur in the midline **[20].** Homer-Wright rosettes are sometimes intermingled and their presence can be associated with high mitotic activity and increased nuclear pleomorphism.

3.3. Desmoplastic/Nodular medulloblastoma.

They comprise small round blue tumor cells, but typically harbor reticulin-free "pale islands" within a reticulin-rich stroma, which are often immunopositive for synaptophysin indicating neuronal differentiation. Desmoplastic/nodular medulloblastomas/MBEN (15%) typically carry a favorable prognosis, and may arise laterally in a cerebellar hemisphere **[21].** They show collagen fibers or other extracellular material visible on routine hematoxylin stains.

3.4. Anaplastic medulloblastoma and large cell medulloblastoma.

Anaplastic medulloblastomas (15%) are characterized by marked nuclear pleomorphism, nuclear molding, and cell-cell wrapping **[20].** Anaplasia grade is defined by four features: 1) increased nuclear size, 2) numerous mitoses, 3)

numerous apoptoses, and 4) either sheets or nodules of large cells with round nuclei and prominent nucleoli (large cell subtype) or angular, crowded, pleomorphic nuclei in large cells.

Large cell variant (2–4%) displays a monomorphous population of large cells whose nuclei exhibit prominent nucleoli. Both variants are characterized by a very high proliferative activity, abundant apoptosis, and a much poorer prognosis [22].

Both large cell and anaplastic variants comprise cells with large, round, vesicular nuclei and prominent nucleoli, from which the large cell variant derives its name.

The majority of medulloblastomas exhibit neuronal differentiation in the form of immunoreactivity to synaptophysin and some also display focal glial differentiation (Glial fibrillary acidic protein (GFAP) immunopositivity) [23]. Rare examples show myogenic differentiation (medullomyoblastoma) or melanotic differentiation [23].

3.5. GENETIC AND MOLECULAR SUBTYPES OF MEDULLOBLASTOMA.

More recently a consensus conference in Boston in 2010 supported classification of four main subgroups of medulloblastomas based on the molecular profiling. Recently, the integrated genomic profiling of MBs was conducted [24] and the results indicate that MB consists of at least four distinct molecular subgroups: WNT, SHH, Group 3, and Group 4 [24].

The Wnt and Shh groups were named after the predominant signaling pathways thought to be affected in their pathogenesis. Less is known currently regarding the pathogenesis of groups 3 (tending to harbor MYC amplification) and 4 (tending to have isochromosome 17q) and therefore generic names were chosen until it is better understood [24].

All four groups show relatively distinct variation in demographics, histology, genetic profile, and clinical outcome.

It is now clear that MB, which was previously considered to be a single disease entity, consists of at least four distinct molecular subgroups, and these subgroups are clinically relevant. Thus, the molecular subgrouping of MB is expected to add significantly to outcome predictions, more than any of the established clinical prognostic markers, such as, age, metastatic stage at diagnosis, extent of resection, and World Health Organization (WHO) classification.

In addition to impacting patients with MB stratification and treatment strategies, the molecular subgrouping of MB will contribute to the identification of subgroup-specific targeted therapies. As discussed earlier, SMO inhibitors have recently been developed and tested on patients with SHH MB, with promising results. Subgroup-specific therapeutics has the potential to be more effective and to have significantly improved safety profiles compared to current standard therapies.

3.6. Wnt MEDULLOBLASTOMAS.

Wnt tumors are thought to be the rarest subgroup of medulloblastoma, accounting for 11% [25] but they have probably been the most studied and have a very good long-term prognosis with overall survivals reaching 90% [26]. Wnt tumors also show a specific age distribution being almost absent in infants (aged <4years) (Figure 1) but predominantly affecting children with a peak incidence of 10-12years (Figure 1) [25].

Wnt tumors are thought to arise from lower rhombic lip progenitors in the dorsal brainstem. They arise from mossy-fiber neuron precursors, which may be involved in the formation of synapses in the developing cerebellum [27].

Germline mutations in the gene encoding the Wnt pathway inhibitor (Figure 2), APC, predispose individuals to develop Turcot syndrome, which increases the risk of

developing MB. The loss of chromosome 6 and activating mutations in the gene encoding β-catenin are commonly found in WNT MBs [23]. Other recurrent somatic mutations are also found in the genes encoding p53, DDX3X, and SMARCA4.

Wnt tumors frequently exhibit classic histology [28]. However, some also exhibit large cell and anaplastic histologies, and these tumors also have a good long-term prognosis. WNT MBs are typically located at the midline of the brain, and occupy the fourth ventricle. They typically infiltrate the brain stem.

The sex ratio for Wnt MBs is 1:1[24] and these MBs are most commonly found in older children and teenagers, and are rarely found in infants. With a very low rate of metastatic spread, it is perhaps unsurprising that 5-year overall survival for Wnt-medulloblastoma exceeds 95 percent, making it the most prognostically favorable molecular subgroups [23]. Thus, current plans for Wnt MB clinical trials are focused on developing therapy de-escalation protocols that maintain the high-cure rates, while diminishing the adverse effects of therapy. These protocols are expected to include dose-reduced craniospinal radiation and/or decreased chemotherapy regimens.

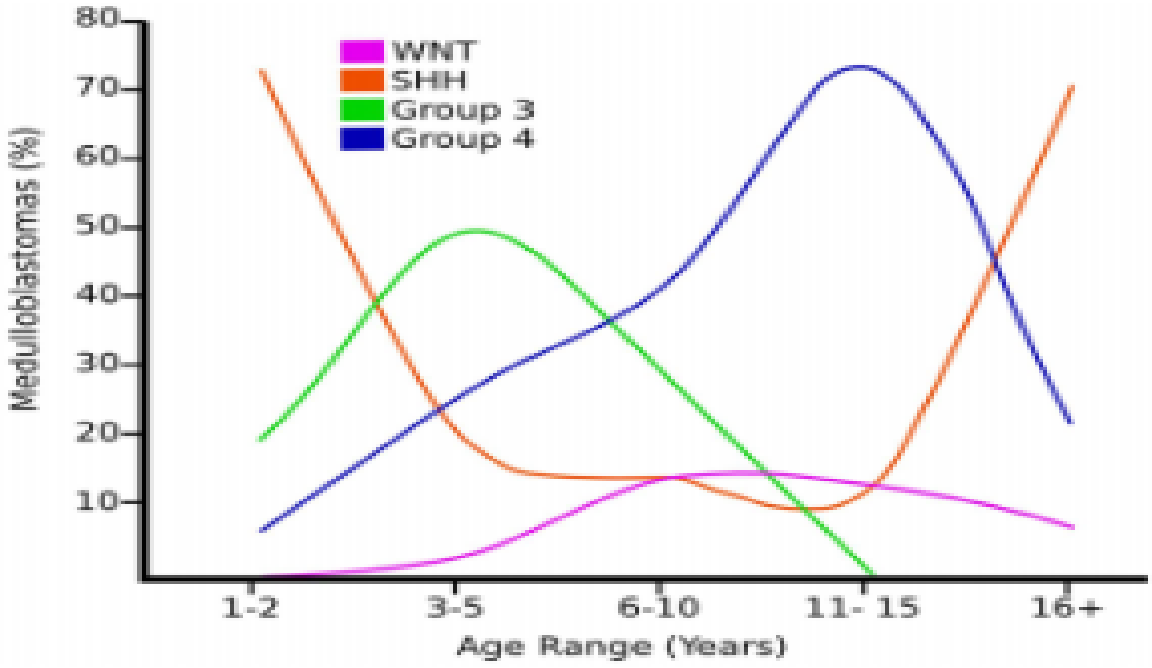


FIGURE 1 Graph showing the age distribution for different subgroups of medulloblastoma.

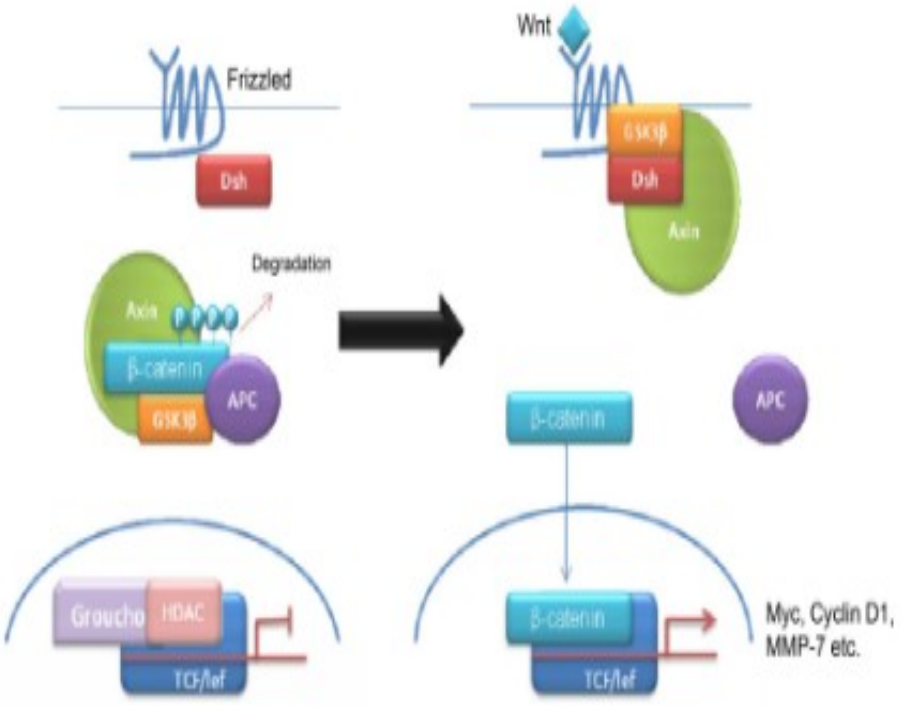


FIGURE 2 : Schematic overviewingWnt signaling.

3.7. Shh MEDULLOBLASTOMAS.

The Shh subgroup accounts for ~30% of all MBs, and is characterized by aberrations in the Shh signaling pathway **[29].** They have an intermediate prognosis between good prognosis Wnt tumors and poor prognosis group 3 tumors, and may be similar in prognosis to group 4 **[30].** Shh medulloblastomas show a dichotomous age distribution being more common in both infants (<4years) and adults (>16years) (Figure 1)**[30].** Shh-medulloblastoma, which is rarely metastatic upon diagnosis and frequently associated with nodular/desmoplastic histology, is considered to have an intermediate prognosis with approximate overall survival ranging from 60 to 80 percent **[31].**

Aberrant Shh signaling (**Figure 3**) in normal human development can cause holoprosencephaly a disorder which affects the midline of the face and nervous system,and there is an increased risk of infant medulloblastoma in Gorlin syndrome, which have germline mutations in PTCH,the Shh receptors**[32].** The sonic hedgehog (Shh) pathway plays a key role in normal cerebellar development where it induces proliferation of neuronal precursor cells in the developing cerebellum and other tissues **[33].** Similarly, individuals with germline mutations in the gene encoding the Shh inhibitor SUFU are predisposed to infantile MB **[29].**

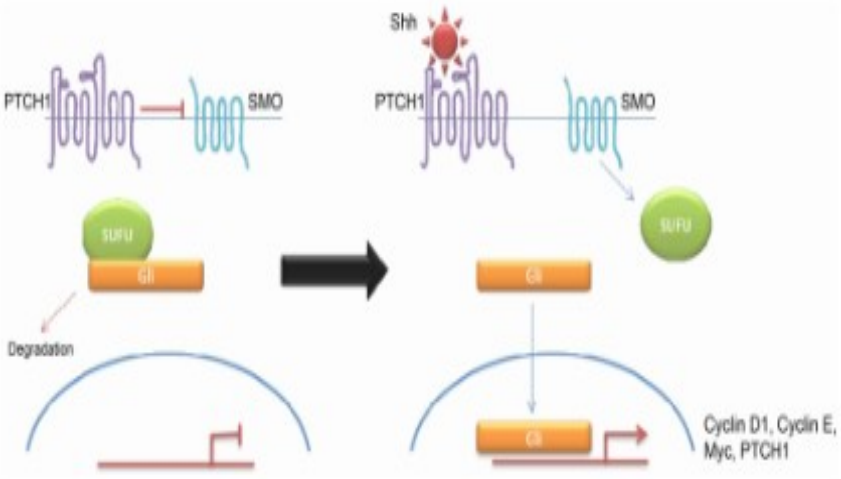


FIGURE 3 : Schematic overviewing Shh signaling.

In addition, somatic mutations in the genes encoding PTCH, SUFU, and the SHH co-receptor, SMO (smoothened homolog), as well as amplification of the genes encoding the GLI1 and GLI2 transcription factors have been found in sporadic MB **[29].** Other somatic mutations in the genes encoding TP53 (p53) and MLL2 (or KMT2D), are found, respectively, in 14 and 12% of the patients with Shh MBs**[34].** Furthermore, Shh MBs are frequently associated with a loss of chromosome 9q, and less frequently associated with a loss of 17p or 10q, or a gain of 3q **[23].**

Shh MBs are frequently present with a nodular desmoplastic histology, although this histology is found in <50% of all Shh MBs, while the remaining Shh MBs exhibit classic histology **[35].**The large cell anaplastic (LCA) histology has also been found in Shh MBs, but it is unclear if this histology is a prognostic indicator for Shh MB.

The sex ratio in Shh MB is 1:1.The tumors are found at the brain midline in infants or in the cerebellar hemispheres in teenagers and adults. Metastasis at tumor presentation is not common. Furthermore, Shh MB exhibits a bimodal age distribution, predominantly affecting infants and adults, and rarely affecting children. As mentioned above, the SHH MBs in infants and adults are clinically and

molecularly distinct **[36].** Notably, metastasis at presentation is a prognostic indicator in adult but not infant SHH MB.

Table 1 Characteristics of each subgroup of MB

	WNT	SHH	Group 3	Group 4
Prevalence	10%	30%	25%	35%
Age	Children, teens	Infants, adults	Infants, children	Infants, children, adults
Sex (M:F)	1:1	1:1	2:1	3:1
Histology	Classic	Nodular desmoplastic histology, classic, LCA	Classic, LCA	Classic, LCA
Metastasis	Low	Low	High	High
Recurrence	Rare	Local	Metastasis	Metastasis
Prognosis	Best	Intermediate	Poor	Intermediate
5-Year OS	95%	75%	50%	75%
Genetics	CTNNB1 DDX3X SMARCA4	MYCN, GLI2, PTCH1, SUFU, MLL2, SMO, TP53, BCOR1, LDB1, GABRG1	MYC, PVT1, OTX2, MLL2, SMARCA4, CHD7	OTX2, DDX31, CHD7, SNCAIP, MYCN, CDK6 GFI1/GFI1B, MLL2, KDM6A, MLL3, ZMYM3
Chromosome	chr 6 loss	chr 3q gain, chr 9q loss, 10q loss	chr 1q gain, chr 5q loss, 10q loss	Isochromosome 17q chr X loss, 17p loss
Cells of origin	Lower rhombic lip progenitors	Cerebellar granule neuron precursors	Neural stem cells?	Upper rhombic lip progenitors

LCA: large cell anaplastic.

3.8. GROUP 3 MEDULLOBLASTOMAS.

Group 3 tumors account for ~25% of all MB cases and have the poorest prognosis of the MB subgroups and are frequently metastatic. Large cell anaplastic medulloblastoma, which has a high propensity for cerebrospinal fluid spread and an aggressive clinical course, is most commonly associated with the molecular subtype of medulloblastoma known as group 3 **[37].**

Rarely found in adults or infants and associated with a mere 40 to 50 percent overall survival, nearly 50 percent of these tumors present with metastatic spread at the time of diagnosis **[34].** Notably, males are approximately 2-fold more likely to be effected with group 3 medulloblastoma than females **[34].**

It may be convenient to consider them as being associated with MYC amplification (not MYCN) but not exclusively [23]. Interestingly, OTX2 had been shown totranscriptionally upregulate the oncogene Myc [38]. 26% of group 3 tumors have isochromosome 17q, however, group 3 tumors are much more likely than group 4 tumors to show gain of chromosome 1q and/or loss of chromosome 5q and chromosome 10q [24]. The 5-year overall survival rates are 45 and 58% for infants and children with Group 3 MB, respectively [23]. Group 3 MB is more common in males than in females, and is observed in infants and children, rarely in teenagers, and never in adults [35]. While pediatric MBs consist of four distinct subgroups, adult MBs consist of only three [23]. The high rate of metastasis associated with Group 3 MBs and their poor prognosis suggest that more effective therapies are needed for patients with these tumors. Further research is required to clarify the underlying mechanisms associated with Group 3 MB and develop novel therapeutic Group 3 tumors are associated with TGF-beta signaling[39],suggesting that strategies targeting TGF-beta signaling pathways might provide safer and more effective treatment options for Group 3 MB.

3.9. GROUP 4 MEDULLOBLASTOMAS.

Group 4 tumors account for ~35% of all MBs, and are the most frequent subgroup. These tumors exhibit an intermediate prognosis, similar to that of the Shh subgroup. However, the underlying biology of Group 4 tumors is less understood than that of the other subgroups.

Group 4 medulloblastomas rarely affect infants (0-3years) and mainly affect children, with a peak age of 10years (table 1) [23] with a sex ratio is 3:1 (male:female) [26]. Although they frequently metastasize in ~35-40% of the cases [34], they still have an intermediate prognosis a 5-year overall survival rate that

exceeds 80%, while patients with high-risk group 4 MB have a 5-year overall survival of ~60% [40], compared with the poor prognosis of group 3[21].

The vast majority of group 4 medulloblastomas have a classic histology, although less frequently they can have a large cell/anaplastic morphology [23].

They are characterized by a collection of genomic alterations that variably occur in conjunction with one another. Amplification of MYCN and cyclin-dependent kinase 6 (table 1), as well as cytogenetic abnormalities to isochromosome 17q and heterozygous loss of the X chromosome in females are all common to group 4 tumors [34]. Previous publications indicate that Group 4 tumors exhibit neuronal gene expression signatures[41] that include mutations in the genes encoding KDM6A, MLL3, and the zinc finger MYM-type protein, ZMYM3. Notably, mutations in KDM6A are the most common mutations in Group 4 MB [28]. Another recurrent genetic alteration in Group 4 tumors is a tandem duplication of the gene encoding synuclein alpha interacting protein (SNCAIP) [39],which is also duplicated in Parkinson's disease.

3.10. CLINICAL RISK STRATIFICATION.

Medulloblastoma was classified clinically by Chang in 1969 based on the size and invasiveness of the tumor as determined intra-operatively and on the presence of metastases [42]. It was determined considering the size, invasiveness, and spread outside the posterior fossa (Table 17.2). Brainstem invasion was considered an important prognostic factor.

The Chang system is no longer used, although elements of it form the current clinical risk stratification of medulloblastoma.

Despite the increase in overall survival following introduction of postoperative craniospinal radiation and chemotherapy in the 1970s, patients

diagnosed before age 3 continue to have a markedly lower survival than older individuals [43].

Table 2 : Clinical staging of medulloblastoma (Chang, 1969).

extent of tumor		
T1	primary tumor <3 cm in diameter	
T2	primary tumor >3 cm in diameter	
T3	primary tumor >3 cm in diameter with radiographic or operative extension beyond the posterior fossa	
	T3a	extension into the aqueduct of Sylvius and/or foramen of Luschka
	T3b	extension into the brainstem
T4	primary tumor >3 cm in diameter with extension past the aqueduct of Sylvius and/or the foramen magnum	
extent of metastasis		
M0	no evidence of gross or microscopic subarachnoid or hematogenous metastases	
M1	microscopic tumor cells present in the cerebrospinal fluid	
M2	gross nodular metastases in the 3rd or 4th ventricles, or within the subarachnoid spaces of the cerebellum and/or cerebrum	
M3	gross nodular metastases in the spinal canal	
M4	systemic metastases outside the cerebrospinal axis	

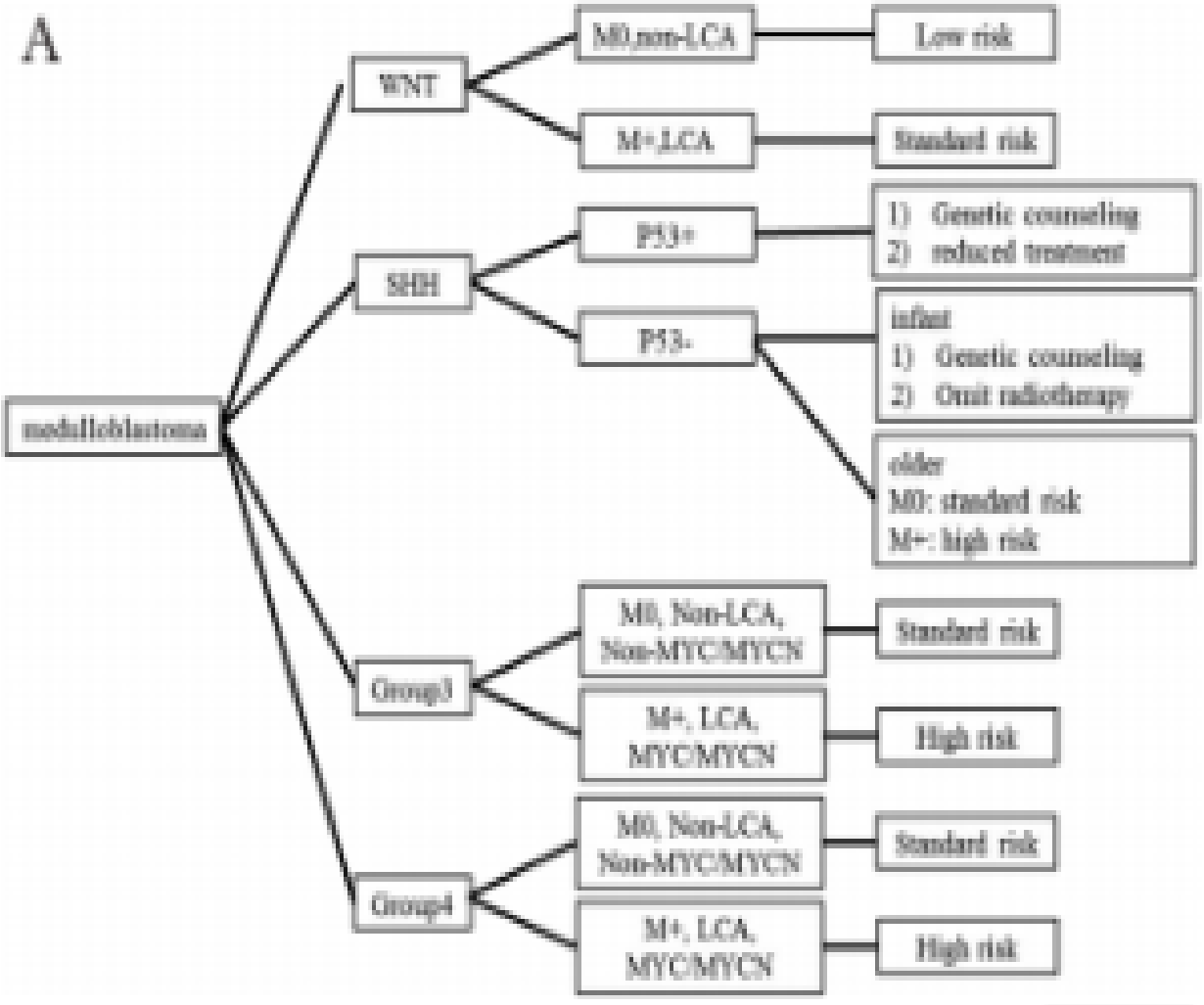
Currently, medulloblastoma is classified clinically into high risk and standard (average) risk, which is summarized in Table 3. The factors contributing to this classification are solely clinical [44]. ;

- Age is a key factor, which may reflect in part the aggressive natural history of tumors in the underthree age group and also reflect the limitations and side effects of therapy.
- Metastases presence or absence
- Resection extent of residual tumor on the most involved computed tomography (CT) axial image following resection.

Table 3 : Risk stratisfication of medulloblastoma.

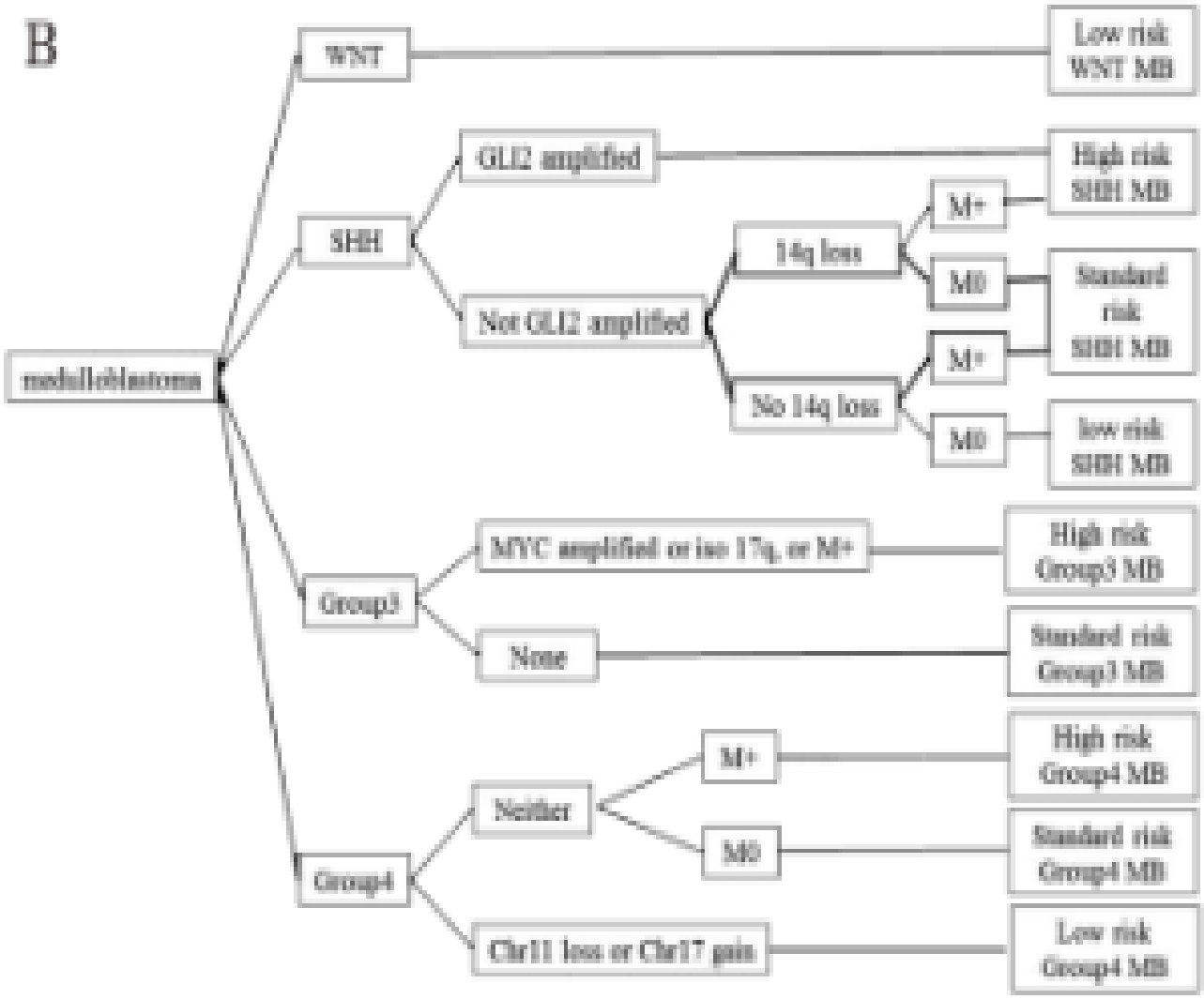
	average risk	high risk
age at diagnosis	≥3 years	≤3 years
extent of residual tumor	≤1.5 cm^2	≥1.5 cm^2
metastatic/disseminated disease	absent	present

Recent studies have proposed new risk stratification systems for MB based on clinical, histological, and molecular variables [40, 45, 46]. These studies suggest that determining the clinical stage (residual tumor, metastasis, and age), histopathological subtype, and molecular subgroup are critical prerequisites for patient-risk stratification and risk-adapted therapeutic strategies.



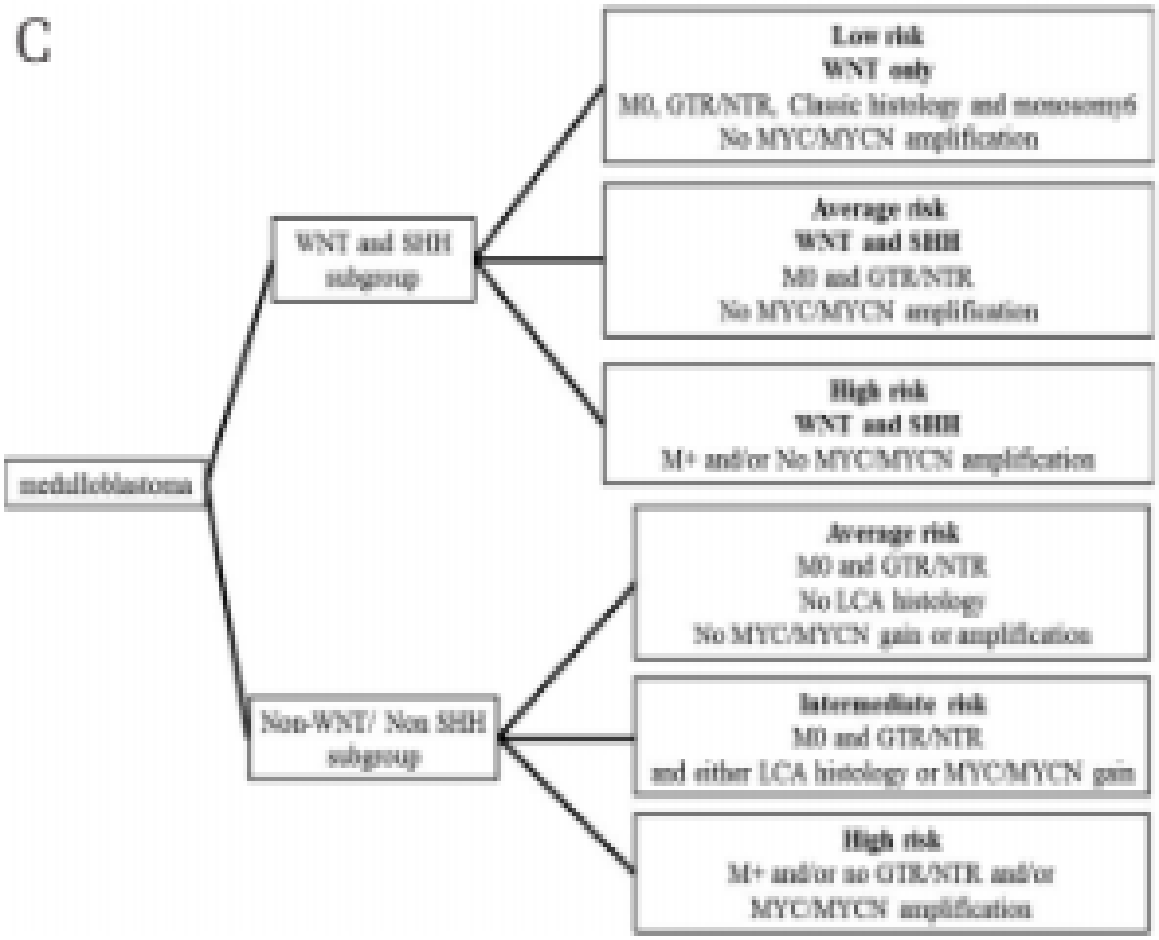
(A) Risk stratification proposed by Pietsch et al. [45]

LCA: large cell anaplastic, M: metastatic status, GTR: gross total resection, NTR: near total resection



(B) Risk stratification proposed by Shih et al. [40]

LCA: large cell anaplastic, M: metastatic status, GTR: gross total resection, NTR: near total resection



(C) Risk stratification proposed by Gottardo et al. [46]

LCA: large cell anaplastic, M: metastatic status, GTR: gross total resection, NTR: near total resection.

Figure 4: newly proposed risk stratification systems for MB patients. (A), (B), (C) according to Piesche et al, Shih et al and Gottardo et al

Recent studies have sought to identify the cells of origin for each subgroup of MB (Table 1). WNT MB is reported to develop from progenitor cells of the lower rhombic lip [27] and SHH MB from cerebellar granule neuron precursors. [47] Group 3 MB is proposed to originate from neural stem cells. The cells of origin of Group 4 MB have long been unknown, but a very recent study suggests that they are progenitors of the upper rhombic lip [48].

The characteristic MRI findings of patients with MB from each subgroup were also recently reported [49, 50]. Most of the Group 3 and Group 4 tumors grow in the vermis and infiltrate the fourth ventricle. WNT MB contacts the brain stem and expands into the fourth ventricle. Conversely, SHH MB grows predominantly in the rostral cerebellar hemisphere. These locations may be related to the cells of origin of each MB subgroup [49, 50].These MRI findings are summarized in Figure 5

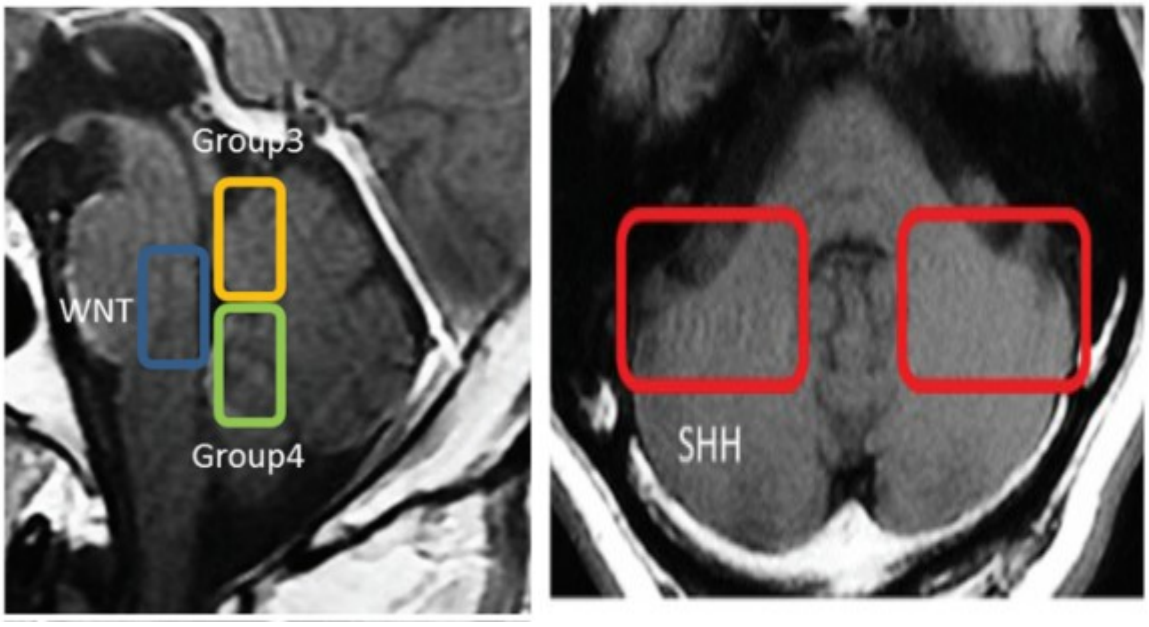


Figure 5 : MB localization of the various MB subgroups.

4. IMAGING CHARACTERISTICS OF MEDULLOBLASTOMA.

Medulloblastoma presents many faces on imaging. The cerebellum is by far the most common location (94.4 %), with most medulloblastomas (75 %) arising in the midline, mainly in the middle and lower vermis.

Dissemination to the cerebrospinal fluid is relatively common at presentation; spinal drop metastases and leptomeningeal tumor dissemination at the time of diagnosis were reported in up to 19.4 % of pediatric medulloblastomas.

Carefully performed CT and MR provide suitable topography and characteristics, but MR is superior in the detection of pre or postoperative neoplastic spread elsewhere in the subarachnoid space. Careful assessment of disease extent is essential in planning both surgical resection and adjuvant therapy, and preoperative imaging of the entire neuraxis is critical given the high propensity of drop metastases.

4.1. Computed Tomography.

The CT typical appearance of a medulloblastoma is a well-defi ned, hyperattenuating, and homogeneous midline vermian mass surrounded by vasogenic edema, associated with hydrocephalus, and marked and homogeneous enhancement on contrast material–enhanced images (Fig 6) [51].

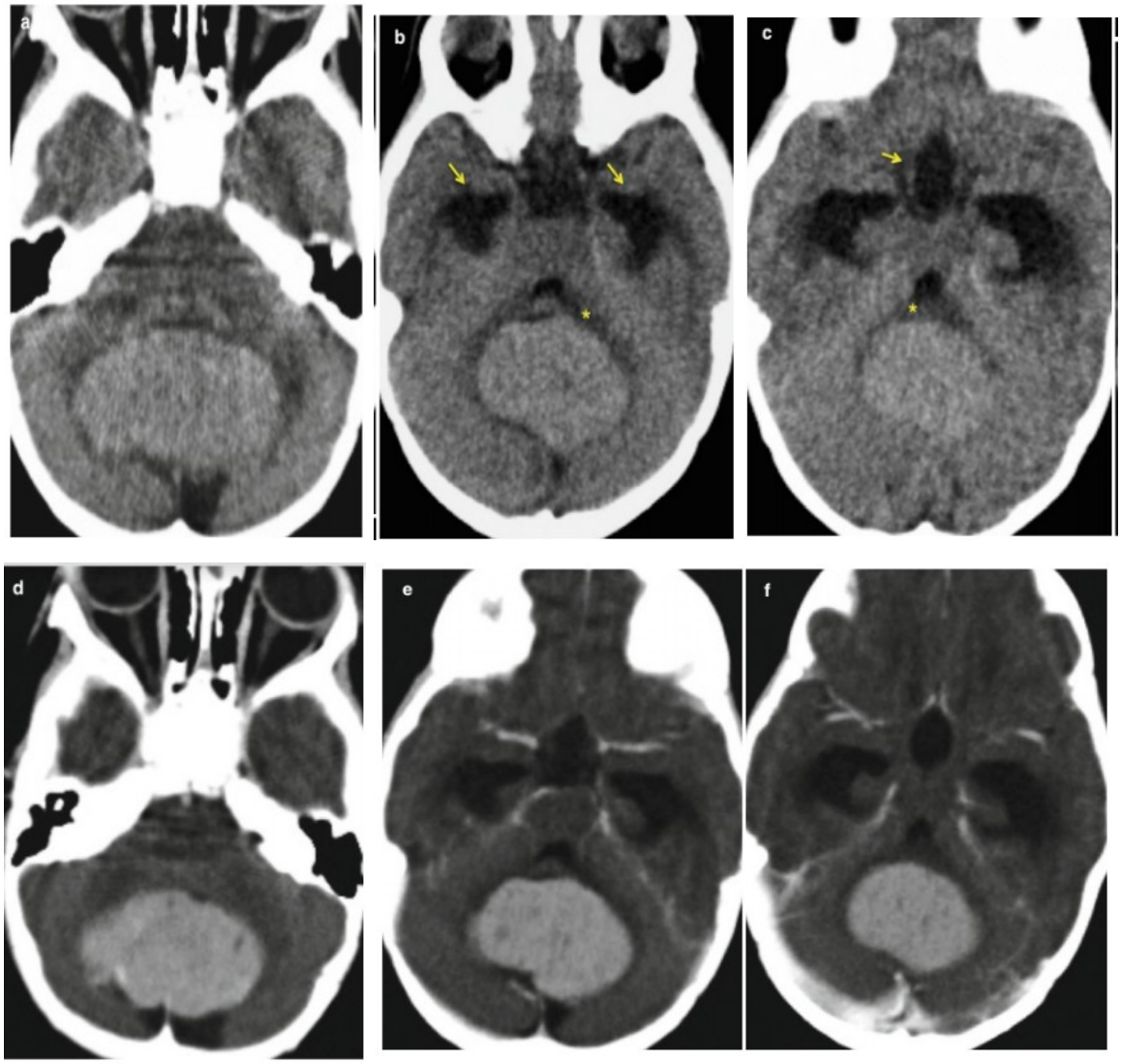


Fig. 6 Typical features of head CT scan:

(a–c) unenhanced CT shows a well-defi ned, homogeneous hyperattenuated mass in the posterior fossa midline surrounded by vasogenic edema (asterisk), associated with hydrocephalus (yellow arrows). (d–f) Contrast-enhanced CT image shows intense, nearly homogeneous enhancement of the mass

From data collected on 420 patients in three studies 89% of all medulloblastomas demonstrated at least some hyperattenuation compared with normal cerebellar attenuation on nonenhanced CT scans **[52, 53, 54]**. A review of 233 patients **[54]**, found that 95% had marginal vasogenic edema and 97% had at least some enhancement.

However, variance from this imaging appearance is common, seen in about 40% of all cases **[53, 54, 55]**. Several series have revealed atypical features which include cystic 30 to 60 % **[51]** presenting either as multiple small cysts or single large cavity. Necrotic regions have also been reported **[54]**, calcification (20–30 %) **[51]**, ill-defined margins and lack of enhancement. Intralesional areas of low density (usually <1 cm), consistent with intratumoral cystic and necrotic degeneration, can be depicted (**Fig.7**)

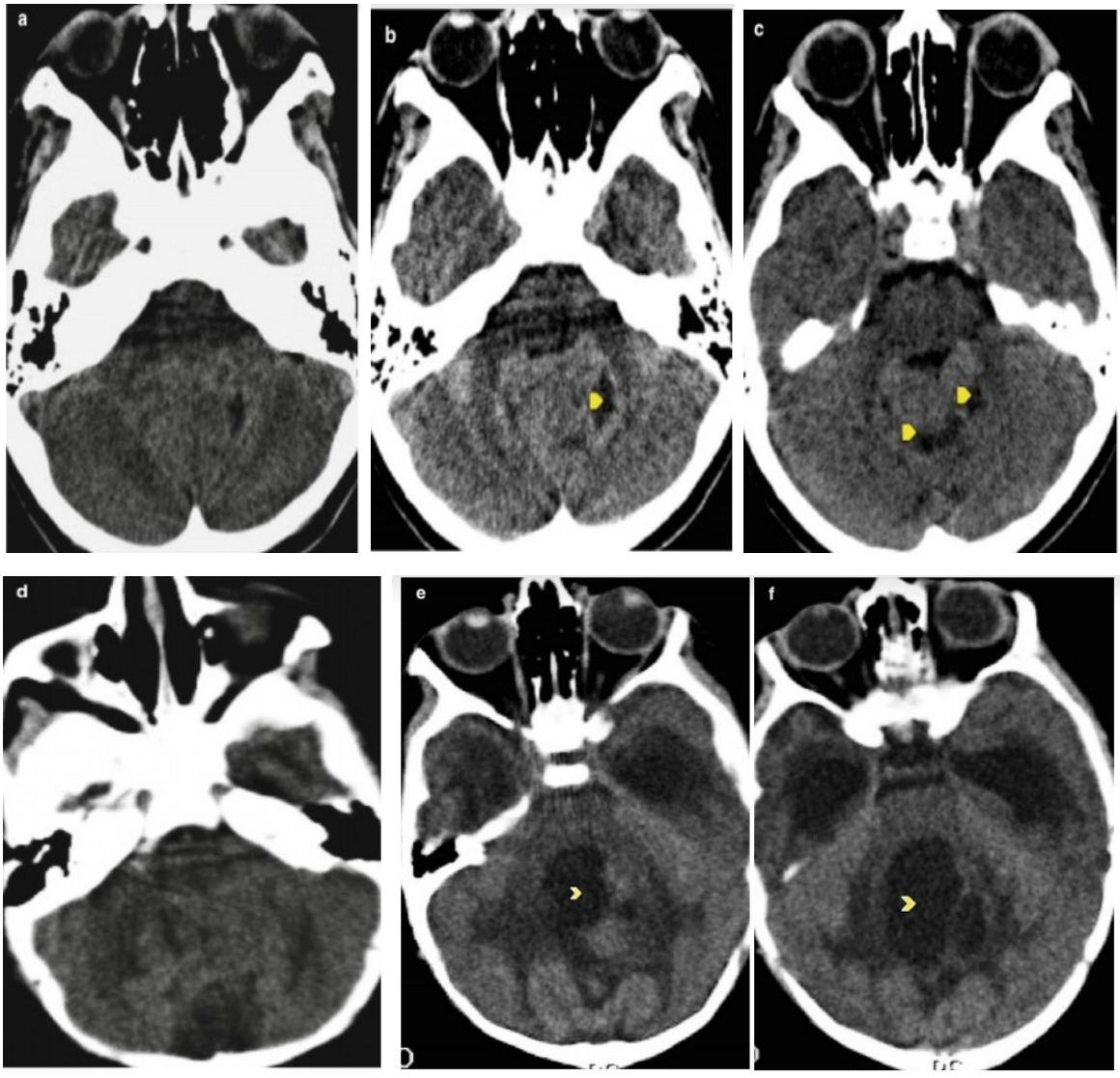


Fig. 7 Variability of medulloblastoma on CT images:

(a–c) unenhanced CT image shows heterogeneous hyperdense mass with cystic/necrotic areas (arrowheads) in the posterior fossa midline. (d–f). On the

unenhanced CT image, the mass is hypo-iysodense compared with the surrounding normal cerebellum, and tumor has small cysts and a large cavity (arrowheads).

Other less common atypical features include, absence of vasogenic edema or hydrocephalus, hypoattenuation, hemorrhage, absence of enhancement on contrast-enhanced images, and the appearance of "primary" leptomeningeal dissemination [51].

Metastatic nodular seeding may be seen in the supratentorial subarachnoid space on contrast-enhanced CT scans and in the spinal canal on CT myelography. In the ventricle, typical area of metastases at diagnosis is the infundibular recess in the third ventricle [51].

Falcine calcification in children with medulloblastoma can suggest a nevoid basal cell carcinoma. For the reason that children with this tumor have a propensity to develop various basal cell carcinomas in irradiated fields, examination with CT in such patients is crucial, since it may influence therapeutic decision in the favor of chemotherapy or reduced-dose radiation therapy [56].

4.2. MAGNETIC RESONANCE.

The standard MRI protocol for pediatric intracranial tumors includes fl uid-attenuated inversion recovery (FLAIR), T1-, T2-, axial diffusion and postcontrast T1-weighted sequences for brain and spine [51]. MR angiography is regularly performed to better clarify the characteristics of the intratumoral circulation and to plan best way for the intervention. Perfusion MRI and proton magnetic resonance (MR) spectroscopy are performed to distinguish post treatment changes from recurrent tumor in the posttherapeutic setting, or when the neoplastic nature of a primary lesion is in question.

Preoperative evaluation of entire neuraxis and postoperative evaluation of surgical bed are key to prognosis (figure 8).

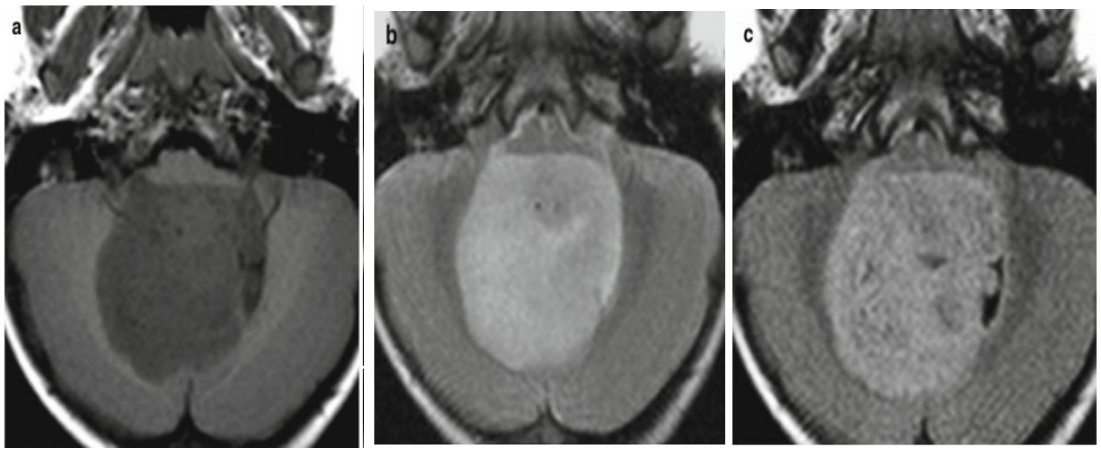


Figure 8 Medulloblastoma. MR typical features:

a. On an axial T1-weighted MR image, the mass is hypointense compared with the surrounding normal cerebellum with well-defi ned margins.
b. On an axial T2-weighted MR image, the mass shows mild hyperintensity compared with surrounding normal brain tissue.
c. On an axial FLAIR MR image, the tumor shows hyperintensity compared with surrounding normal brain tissue with well defined margins.

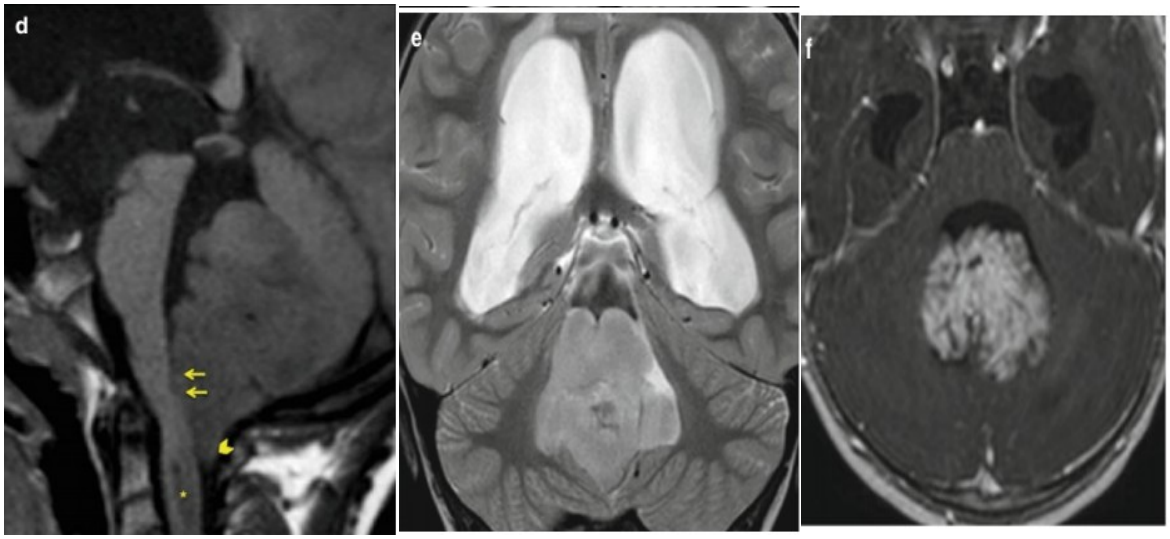


Figure 8 (continued)

d. Sagittal T1-weighted MR image shows ill-defi ned mass originating from the inferior medullary velum compressing the fourth V and brainstem (arrows), causing obstructive hydrocephalus and projecting through the foramen magnum (arrowheads). Notice the hyposignal at C2-C3 level due to compression effect (asterisk).

e. On a coronal T2-weighted image, the mass shows hyperintensity and hydrocephalic dilatation of the lateral ventricles.

f. Contrast-enhanced axial T1-weighted MR image shows intense, nearly homogeneous enhancement of the mass.

Medulloblastomas are most commonly situated in the region of the fourth ventricle as midline lesions involving the anterior portion of the vermis and originates from the inferior medullary velum; often the medulloblastomas are located in the middle and lower segments of the vermis. Less frequently can be seen originating from the superior zone of the vermis (figure 9) **[57].**

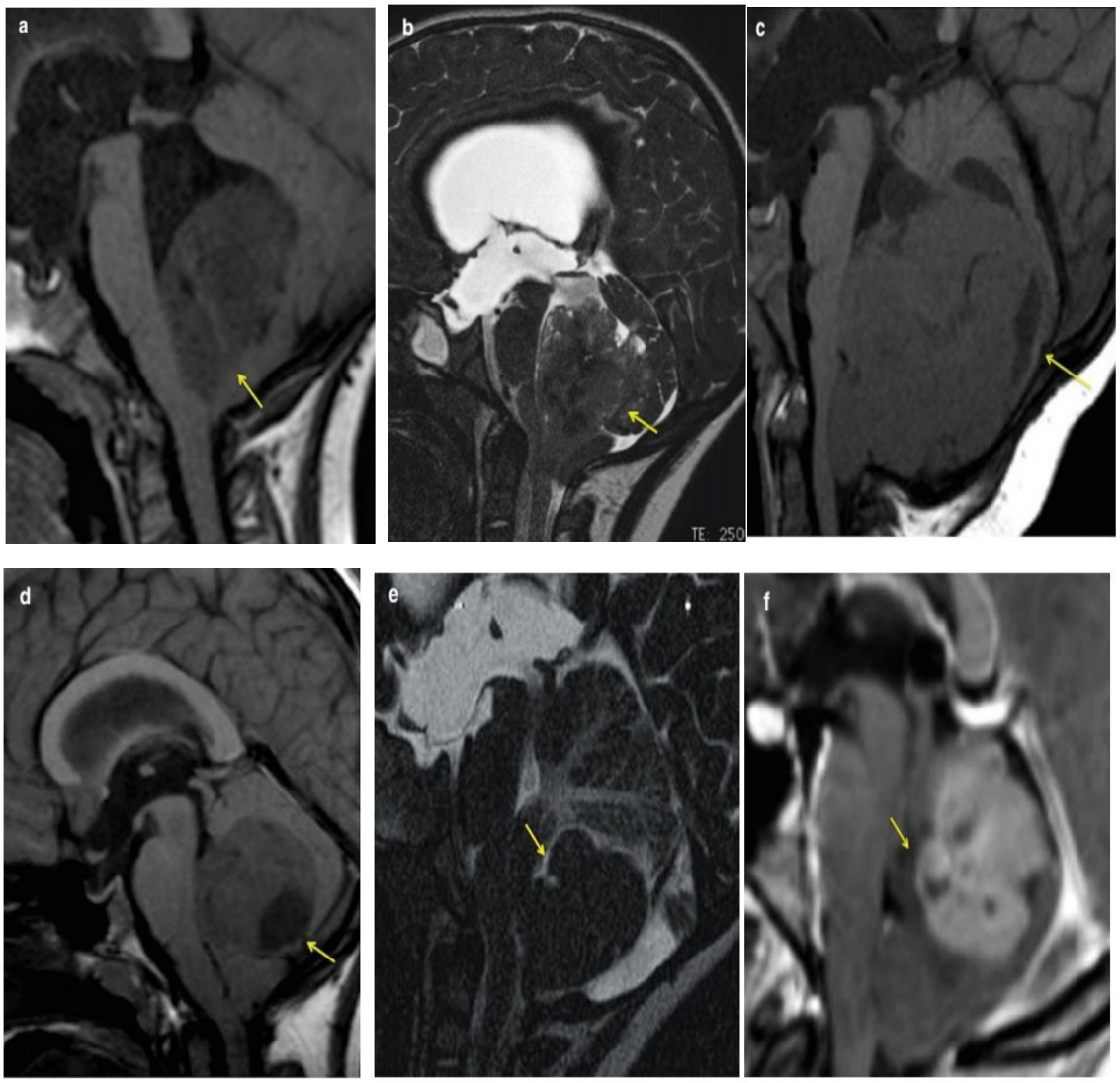
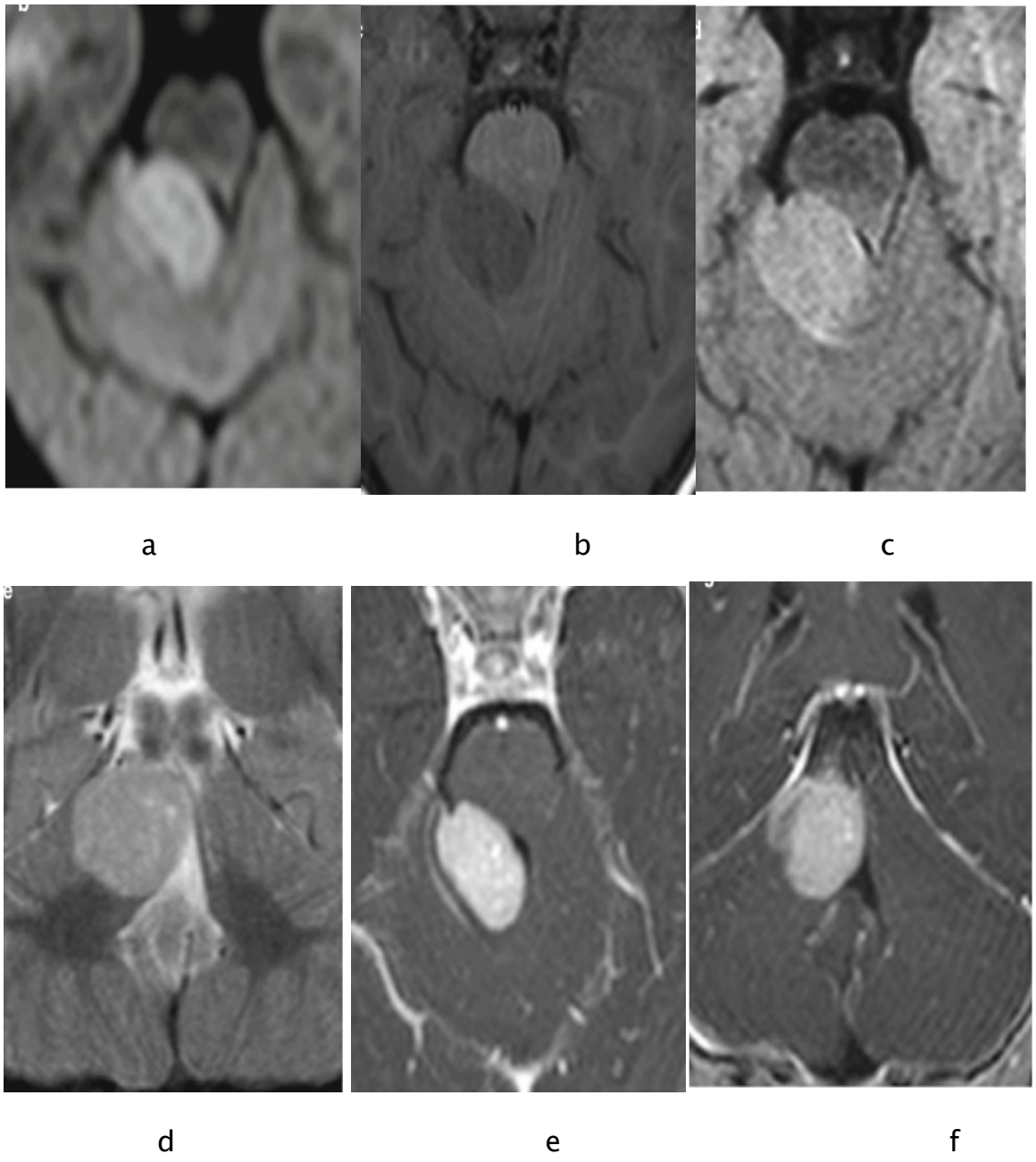


Figure 9 Medulloblastomas in the region of the fourth ventricle originating from the inferior medullary velum (a–c) and mild vermis (d). Medulloblastomas originating from the posterior portion of the vermis (e, f), involving the inferior zone of the vermis (e) and the superior zone of the vermis (yellow arrows) (f).

Medulloblastomas can be also off-midline tumors (figure 10), located in cerebellar hemispheres. An off-midline location is common in desmoplastic medulloblastomas and slightly more common in medulloblastomas with extensive nodularity variants.



a b c

d e f

Figure 10 Medulloblastoma in cerebellar hemisphere:

Desmoplastic MB in a 1-year-old girl (a) Axial DWI MR shows the tumor diffusivity to be increased to that in white matter. (b) On axial T1-weighted MR image, the lesion is hypointense compared with normal cerebellum with well-d efi ned margins. (c) Axial FLAIR MR image shows hyperintensity compared with surrounding normal brain tissue. (d) Coronal T2-weighted MR image shows

hyperintensity compared with surrounding normal brain tissue. (e) Axial T1 C+ MR and (f) coronal T1 C+ MR show intense, homogeneous enhancement of the mass

Foraminal extension from the fourth ventricle to involve the cerebellopontine angle, cisterna magna, and other cisternal compartments may occur but is not common **[58].** Some reported cases of medulloblastoma involved the porus acusticus and simulated the imaging features of a vestibular schwannoma **[59].**

Conventional MR imaging, the classic appearance of a medulloblastoma is iso- to hypointense relative to gray matter with T1W sequences and variable signal intensity relative to grey matter with long repetition time pulse sequences.

The classic MB and anaplastic medulloblastomas show commonly hyperintense signal on T2W images; Desmoblastic MB and MBEN show commonly iso- to hyperintense signal on T2W images (Fig.15.8) **[60].**

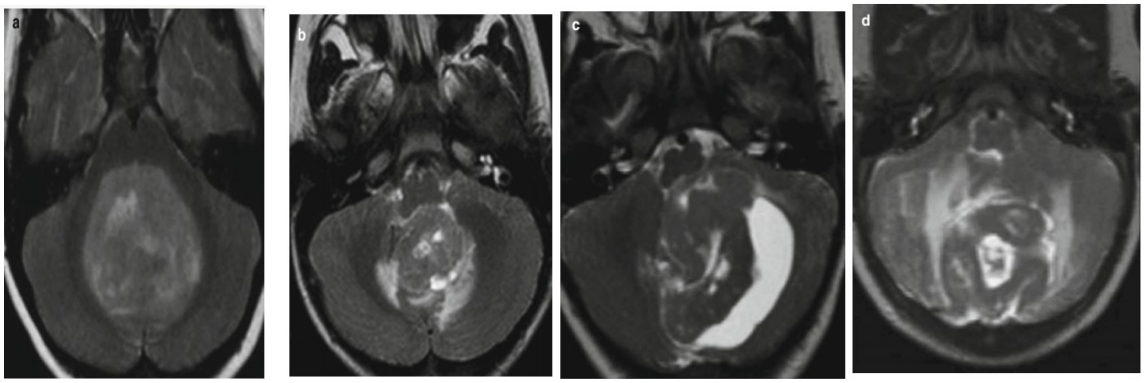


Fig. 11 Variability of signal intensity on T2-weighted images:

a. Axial T2-weighted image shows a nearly heterogeneous hyperintense mass in the posterior fossa midline.
b. On an axial T2-weighted MR image, the mass is hypo-isointense compared with the surrounding normal cerebellum with perilesional edema and well-defined margins.
c. Desmoplastic medulloblastoma: on an axial T2-weighted image, the mass, situated off-midline shows solid and fl uid components, with iso-

hyperintense signal of solid portion compared with surrounding normal brain tissue.

d. Medulloblastoma with extensive nodularity: on an axial T2-weighted image, the mass is heterogeneous isointense with nodular aspect surrounding of vasogenic edema.

Postcontrast images, majority of MB and medulloblastoma variants have a marked enhancement; in classic MB, subtle, marginal, or only linear enhancement is also possible. Large cell (LC) and anaplastic variants show often inhomogeneous but marked enhancement, with or without necrosis and cystic parts; Desmoblastic MB will show a wide spectrum of enhancement patterns, inhomogeneous, marked homogeneous, nodular appearance [60].

At the time of the diagnosis, MBs are commonly associated with hydrocephalus and herniation of cerebellar tonsils.

However, conventional MRI has low sensibility and specificity in identifying specific medulloblastoma types and often cannot reliably differentiate between high-grade and low-grade tumors.

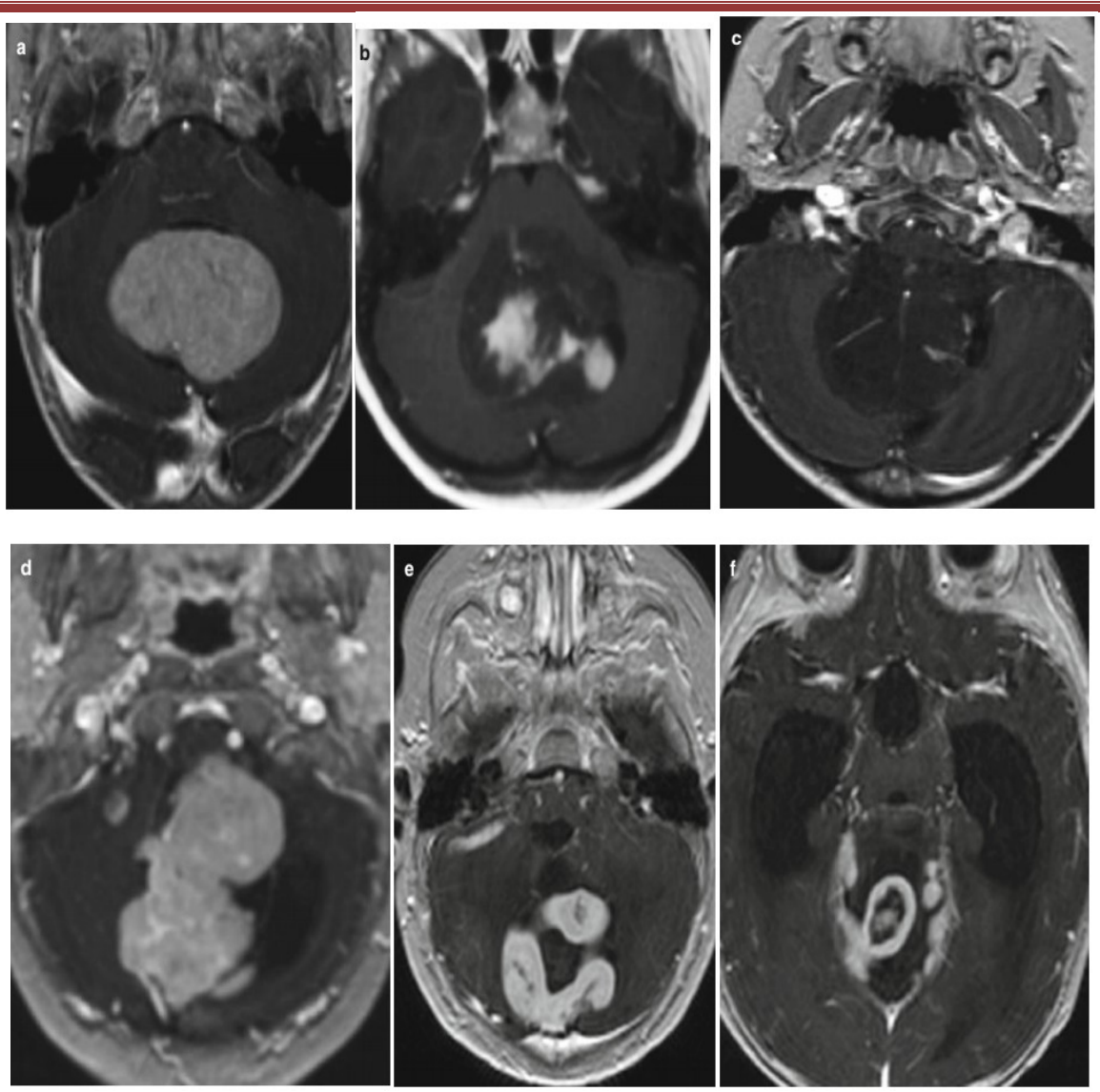


Figure 12: Variability of contrast enhancement.

a. On an axial T1-weighted postcontrast image, medulloblastoma infant shows nearly homogeneous enhancement of the mass.

(b.c) an axial T1-weighted postcontrast image, classic medulloblastoma shows patchy (b) and linear (c) enhancement.

d. Desmoplastic medulloblastoma: on an axial T1-weighted postcontrast image, the mass shows marked homogeneous enhancement with nodular aspect; notice nodular enhancement at the level of the right tonsilla cerebellar.

(e.f) Medulloblastoma with extensive nodularity: on axial T1-weighted postcontrast images, the mass shows multifocal, heterogeneous enhancing, grape- like tumor nodules, and it is possible to depict a central "scar-like" enhancement.

Diffusion-weighted imaging (DWI), apparent diffusion coefficient (ADC) maps, proton magnetic resonance spectroscopy (MRS), and perfusion imaging offer additional informations helpful to determining tumor type and grade.

DWI is used to distinguish necrosis from cyst formation or edema and has shown some effi ciency in identifying different tumor types and delimiting their boundaries against normal cerebral tissue. The densely cellular nature of medulloblastoma and the high nuclear to cytoplasm ratio lead to restriction of the water diffusion, resulting in high signal on trace DWI and low ADC values.

Based on limited results, MBEN and desmoblastic MB may have a lower ADC compared to classic or LCA variants.

Low tumor ADC values compared with normal brain parenchyma have been linked to hypercellularity of the tumors. The high cellularity of medulloblastoma is a well-known histologic feature of these tumors **[61, 62].**

MR sensitivity for leptomeningeal metastases increases with higher doses of contrast and the use of volumetric gradient-echo imaging to obtain thin section axial imaging of the spine. Small metastases on nerve roots can be detected if thin sections (3 mm or less) are used.

All MB show a consistent and significant elevation of Taurine (Tau) at 3.3 ppm and a significant increase in Cho **(Figure 14).** Tau seems associated with an increased cellular proliferation and tumoral aggressiveness.

Elevated taurine (Tau), an amino acid that has not been detected with long TE MR spectroscopy, has recently been observed independently in medulloblastoma by

several groups using short TE MR spectroscopy and was found to be an important differentiator of this tumor type from other common pediatric brain tumors.

High grade tumors which are highly cellularized and have a high proliferative rate show increased Choline levels in comparison to normal brain tissue. In a pediatric population, high levels seemed to correlate with tumor progression and a faster growth.

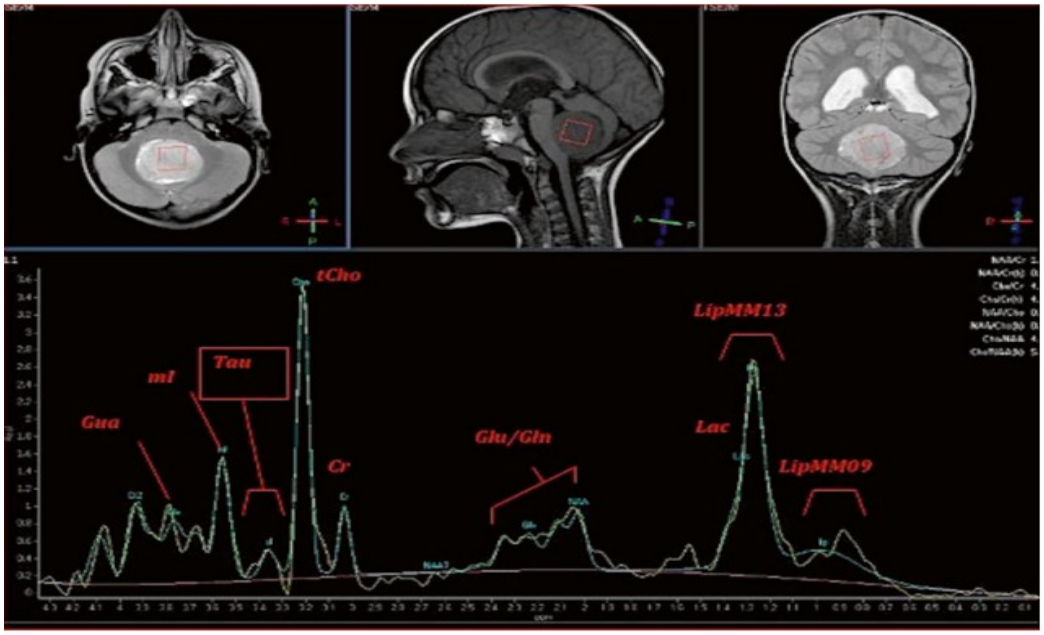


Fig. 13 Short TE (31 ms) 1H-MR spectroscopy of medulloblastoma:

1H spectrum of a solid-appearing medulloblastoma and corresponding T2-weighted transverse and coronal fast spin-echo MR images, T1-weighted sagittal spin-echo MR image, indicating the region of interest. Absolute quantitation included a correction for the fraction of cystic tissue (about 6 %). A singlet at 3.78 ppm consistent with guanidinoacetate (Gua) is observed, and taurine (Tau) is detected as a complex signal intensity at 3.4 ppm.

Spectrum also exhibit broad lipid and macromolecule resonances at 0.9 and 1.3 ppm. One peak of the lactate (Lac) doublet at 1.33 ppm is detected as a shoulder of the broad LipMM13 resonance. N -acetylaspartate (NAA) is depleted, and total choline (tCho) is prominent in all spectra of medulloblastoma

Subarachnoid seeding is common, occurring in up to 33 % of all patients at the time of initial diagnosis **[63].** Evidence of spread of medulloblastoma cells into the CSF is a key factor in staging, prognosis, and treatment.

Subarachnoid spread of disease can be detected by MRI or by CSF cytologic studies. MRI imaging and CSF cytologic analysis should be used in combination to establish the diagnosis. Because the normal flow of CSF from the cisterna magna travels first along the posterior margin of the spinal cord before returning to the cistern along the ventral surface of the spinal cord, most metastases are found along the posterior margin of the spinal cord as the greatest concentration of malignant cells would be expected to be found there **[64, 65].**

Imaging manifestations of leptomeningeal spread of disease in the spine are variable and include:

- smooth enhancement along the surface of the spinal cord
- Nodular enhancement in the extramedullary intradural or, occasionally, intramedullary space **[65].**
- Nerve root thickening, nodularity, or clumping; and thecal sac irregularity.

The lumbosacral region, particularly the most caudal aspect of the thecal sac, is the most common location for “drop” metastases (**Figure 13**).

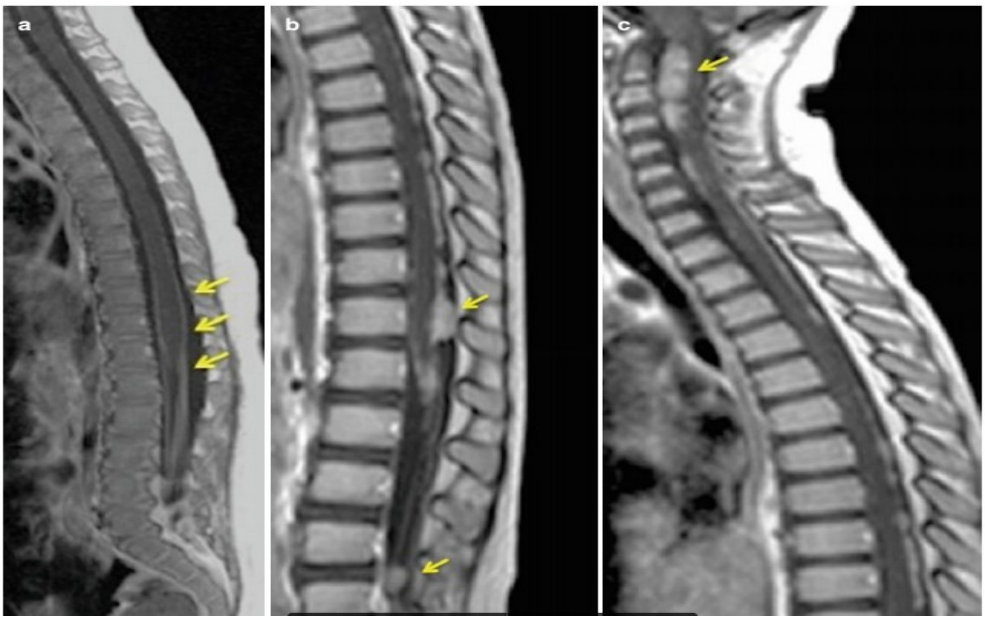


Figure 14 Leptomeningeal spread:

(a) Postcontrast sagittal T1-weighted image show smooth enhancement along the surface of spinal cord in the lumbosacral region (arrows). Postcontrast sagittal (b) T1-weighted images of nodular enhancement in the extramedullary intradural space (arrows). (c) Intramedullary nodular enhancement.

The most common locations for intracranial metastases are the vermian cisterns, the floor of the third ventricle, subependymal region of the lateral ventricles, and subfrontal region **(Figure 15).**

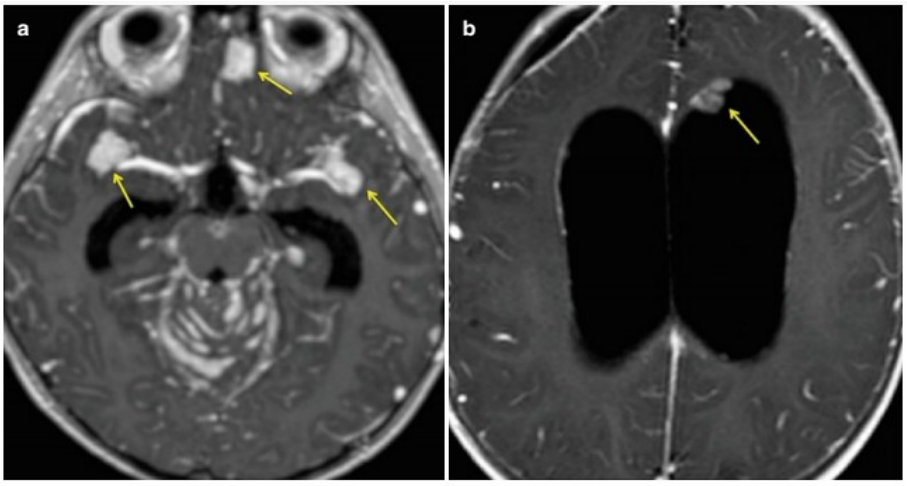


Figure. 15 (a) Axial T1-weighted postcontrast images in metastatic medulloblastoma with cerebellar leptomenigeal enhancement and nodular intracranial metastases in subfrontal and temporal region (arrows); (b) Axial T1-weighted postcontrast images in metastatic medulloblastoma with a lesion in the subependymal region of the lateral ventricules (arrow).

5. CLINICAL PRESENTATION.

Medulloblastomas are mostly located in trhe posterior fossa. Clinical symptoms are usauslly related to neural structures of the posterior fossa including the brainstem, cranial nerves, and the cerebellum.

5.1. Ataxia and Hypotonia

Ataxia refers to a disturbance in the smooth performance of voluntary motor acts. Ataxia may affect the limbs, the trunk, or gait and may be of acute onset, episodic, or progressive.

Typically patients with cerebellar disease have a wide based stance and a gait characterized by staggering and impaired tandem walking **[66].**

- *Truncal instability* may be manifested by falls in any direction. Truncal ataxia and titubations suggest midline cerebellar tumors. It is manifested by a tendency to fall frequently and a widely based gait.

5.2. Hemicerebellar syndrome

Involves limb ataxia, nystagmus, and dysmetria **[67].** The childhood cerebellar tumor most often presents a truncal ataxia, even when the bulk of the tumor is hemispheral rather than vermian.

In hemispheral tumors with ipsilateral hypotonia, there is a marked tendency to fall to the side of the tumor. In vermian tumors or hemispheral tumors with marked hydrocephalus, hypotonia may be most marked in both legs with a tendency to fall in place rather than to either side.

Increased tone in the extremities indicates brainstem compression or actual invasion of the brainstem by the cerebellar tumor. Truncal ataxia combined with spasticity, in the absence of intracranial hypertension, should suggest intrinsic glioma of the brainstem rather than cerebellar tumor **[67].**

5.3. Rapid Alternating Movements

- **Dysmetria**: The ability of the patient to touch their index fingertips together in front of them with their eyes closed should be tested. The abnormality of both range and direction.

Finger/nose test: The patients' ability to touch the tip of their nose and then the examiner's index finger is tested. In this test mild incoordination, terminal intention tremor, and dysmetria can be more readily detected.

Heel/knee/shin test: The patient is asked to place the tip of the heel on the tibial tubercle of the leg and run the heel down the front of the shin. The heel is then lifted off and replaced on the tibial tubercle.

- **Asynergia**: lack of synergy of the various muscle components in performing more complex movements.
- **Dysdiadochokinesia:** impaired performance of rapidly alternating movements and past pointing. Rapid alternating movements, like a patient tapping himself on the back of one hand as fast as he can or tapping his foot on the fl oor or against the examiner's hand, detect fragmentation of movement or inaccuracy of movement, which is accentuated by the speed at which the movement is attempted

5.4. Tremor.

Action or intention tremor: nonrhythmic tremor that appears on action, which is also known as

Terminal intention tremor: At rest the limbs are still, but in action tremulousness appears, which is maximal at the beginning and end of the range of movement.

Truncal tremor can also occur. When sitting or standing these muscles are already in action, and a tremor of the trunk will appear and may become so violent that constant jerking movements of the head and body may occur, which may be backward and forward or even include lateral flexion or rotational movement.

5.5. The Reflex Signs.

The usual cerebellar tumor results in hypoactive deep tendon reflexes, especially in the lower extremities [67. Plantar reflexes are normal.

Hyperactive reflexes, a Babinski sign, or evidence of spasticity points to brainstem compression by the cerebellar tumor.

5.6. Torticollis and Neck Stiffness.

- Torticollis is a hyperkinesia characterized by tonic or clonic contraction of the neck musculature, especially the sternocleidomastoid and trapezius muscles. Torticollis may occur as a sign of a posterior fossa tumor.
- Stiff neck may be due to herniation of a cerebellar tonsil or extension of tumor through the foramen magnum into the upper cervical canal. Neck stiffness tends to increase as intracranial pressure becomes marked.

5.7. Cerebellar Mutism.

This sign is mostly seen after neurosurgical operations; however, it is also rarely seen in patients with posterior fossa tumors preoperatively. A tumor-related mutism in an adult subject has been described **[68].**

5.8. Eye Abnormalities.

- Abducens Nerve Palsy

Lesions of the abducens nerve cause impaired ipsilateral lateral gaze. Therefore, patients with unilateral abducens palsy complain of horizontal diplopia, worst in the direction of the paretic lateral rectus muscle.

Brainstem lesions (abducens nuclear lesions) produce a conjugate (both eyes involved) horizontal gaze palsy toward the side of the lesion, often associated with other neurologic signs of injury to the pons (usually ipsilateral peripheral CN VII palsy.

In cerebellar tumors, abducens palsy with resultant diplopia is usually the result of increased intracranial pressure rather than direct brainstem compression by the cerebellar tumor. Compression of the dorsolateral pons can produce a facial asymmetry. Actual extension of cerebellar tumor into the brainstem can produce other cranial palsies.

- Nystagmus

Instability of gaze characterized by continuous movement of the eyes in any plane.

Pendular nystagmus: When both arcs of the movement are of equal amplitude and the frequency is slow. In most circumstances it is indicative of diminished visual acuity.

Jerk nystagmus: If the amplitude of the movements is unequal and the frequency is rapid, the abnormality.

Abnormalities involving the vestibular system result in jerk nystagmus.

Gaze- evoked jerk nystagmus indicates vestibular abnormalities, whereas vertical nystagmus is indicative of brainstem dysfunction.

If gaze- evoked nystagmus is unilateral, it may indicate ipsilateral cerebellar or brainstem pathology; if bilateral it is of limited localizing value.

Downbeat nystagmus is the most common cause is type I Chiari malformation and other surgically treatable pathology involving craniocervical junction must be excluded.

Upbeat nystagmus is much less common and is usually due to a focal gray matter lesion either at the pontomesencephalic or pontomedullary junction **[69].** Up-beating vertical nystagmus shows a high correlation with lesions of the cerebellar vermis and is often seen in children with medulloblastomas.

Torsional nystagmus is usually due to a lesion of the lateral medulla involving the vestibular nucleus although other brainstem sites of pathology may also be responsible.Usually associated with midline mesodiencephalic or hypothalamic tumor or other pathology in this region.

5.9. Midbrain Syndromes Associated with Tumors.

Midbrain compression is usually due to a supratentorial- transtentorial process (e.g uncal herniation), rather than due to a posterior fossa mass.

- Internuclear ophthalmoplegia – paralysis of the adducting eye on attempted lateral gaze but preservation of convergence. Usually bilateral and often associated vertical nystagmus (MLF syndrome) indicates an intra-brainstem lesion.

5.10. Pontine Syndromes Associated with Tumors.

Lesions in the basis pontis cause a paralysis which eventually shows

- Hypertonus due to interruption of the corticospinal tracts.
- Aataxia due to damage of the pontocerebellar tracts.
- Frequently paralysis of facial and lateral rectus muscles due to interruption of the facial and abducens tracts.

In the tegmentum: when tumors infiltrate the tegmentum, an abducens and an ipsilateral gaze palsy will usually occur together.

Several classical pontine syndromes have been described.

Dorsolateral pontine syndrome (Foville's syndrome); there is an ipsilateral gaze palsy and a contralateral hemiplegia; this results from involvement of both the basis and the tegmentum of the pons on one side.

Millard-Gubler or the ventral pontine syndrome is manifested by an ipsilateral facial and abducens palsy and a contralateral hemiplegia.

5.11. Symptoms Associated with Posterior Fossa Tumors

Headache

This is the most common symptom in patients with posterior fossa tumors. Headache is insidious and intermittent. It is most severe in the morning or after a

nap because of increased intracranial pressure from recumbency and hypoventilation during sleep. Associated neck pain, stiffness, or head tilt suggest tonsillar herniation into the foramen magnum. Headache manifests in children as irritability and diffi culty to be handled.

Nausea and Vomiting

Vomiting may occur, usually in the morning. Vomiting sometimes relieves headache

Strabismus

It is secondary to sixth nerve palsies from intracranial hypertension. Third nerve palsies may also occur.

Lethargy

Lethargy is a common symptom and it was .Young children may not complain of headache or diplopia.

Hydrocephalus and Macrocephaly

Children with posterior fossa tumors tend to present with a shorter duration of symptoms than supratentorial tumors secondary to early obstruction of cerebrospinal fl uid (CSF) pathways.

In the first 6 months of life, the most common presenting signs are the signs of increased intracranial pressure and hydrocephalus.

These infants are more likely to present with macrocephaly because their immature cranial vaults have the ability to accommodate the increased volume caused by the tumor, hydrocephalus, or a combination of both.

The intracranial hypertension and hydrocephalus may also contribute to the development of nystagmus, sundowning, and misalignment of the eyes. In addition, less specifi c complaints of emesis, lethargy, irritability, and poor feeding were more common than focal findings and seizures.

Seizures

Posterior fossa tumors rarely can present with epilepsy. Hemifacial spasm in an infant due to fourth ventricular ganglioglioma has been described. Severe brainstem compression, sometimes occurring during a hydrocephalic attack with an acute rise in intracranial pressure, can produce sudden and episodic extensor rigidity. The patient assumes the decerebrate posture, with autonomic instability, pupillary dilatation, and deep coma.

Cerebellopontine Angle Syndrome.

Gradual unilateral deafness over months or years, with tinnitus, imbalance, and facial asymmetry are commonly noted. Intracranial hypertension is late, in contrast to the cerebellar tumors.

6. MANAGEMENT OF MEDULLOBLASTOMA.

Medulloblastoma therapy has evolved to include surgery, radiation therapy and adjuvant chemotherapy. Prognosis of medulloblastoma has improved over the last two decades, for these reasons.

6.1. SURGERY

Surgery retains a key role in the management of these tumors, so much that extent of surgical resection is one of the main factors affecting the prognosis. Residual tumor after resection greater than 1.5 mm2 may lead to a worse prognosis **[70].** There is not a role for biopsy if the medulloblastoma diagnosis is supported by radiographic evidence.

The goals of medulloblastoma surgery are to treat

- associated hydrocephalus
- Obtain tissue sample for diagnosis and molecular investigations.

- Decompress the brain stem, remove as much tumor as possible (with the aim of complete or near complete removal).

Medulloblastoma is not always completely resectable in cases with extensive and deep infiltration of the fourth v entricle floor, it is preferable to leave residual tumor, rather than cause neurological deficit.

6.2. Surgical considerations

Approximately 85 % of medulloblastomas are located in the cerebellar midline, typically arising from the inferior medullary velum. Microsurgical anatomy of this region has been reviewed in detail by Mussi and Rhoton **[71].**

Inferior medullary velum.

The inferior medullary velum, together with the tela choroidea, forms the inferior half of the roof of the fourth ventricle (Fig.16). It is a thin semitranslucent butterfly shaped sheet of neural tissue connecting the inferior vermis (uvula and nodule) with the two cerebellar hemispheres at the level of the flocculi (Fig. 16)

Laterally it blends into the dorsal margin of the lateral recesses.

Caudally it is attached to the tela choroidea, which forms the lower portion of the inferior half of the roof of the fourth ventricle. The junction between the inferior medullary velum and the tela choroidea (telovelar junction) is at the level of the lateral recess.

The tela choroidea (two thin arachnoid like membranes sandwiching a vascular layer of choroidal vessels to which choroid plexus is attached) opens in three points in the subarachnoid spaces recesses forming the two foramina of Luschka and in the midline forming the foramen of Magendie.

The external surface of the caudal half of the roof lies in the deep of the cerebellomedullary fissure. This is a complex cleft that extends between the cerebellum and the medulla and communicates around the tonsils (paired ovoid

structures attached to the cerebellar hemispheres along their superolateral borders) with the cisterna magna.

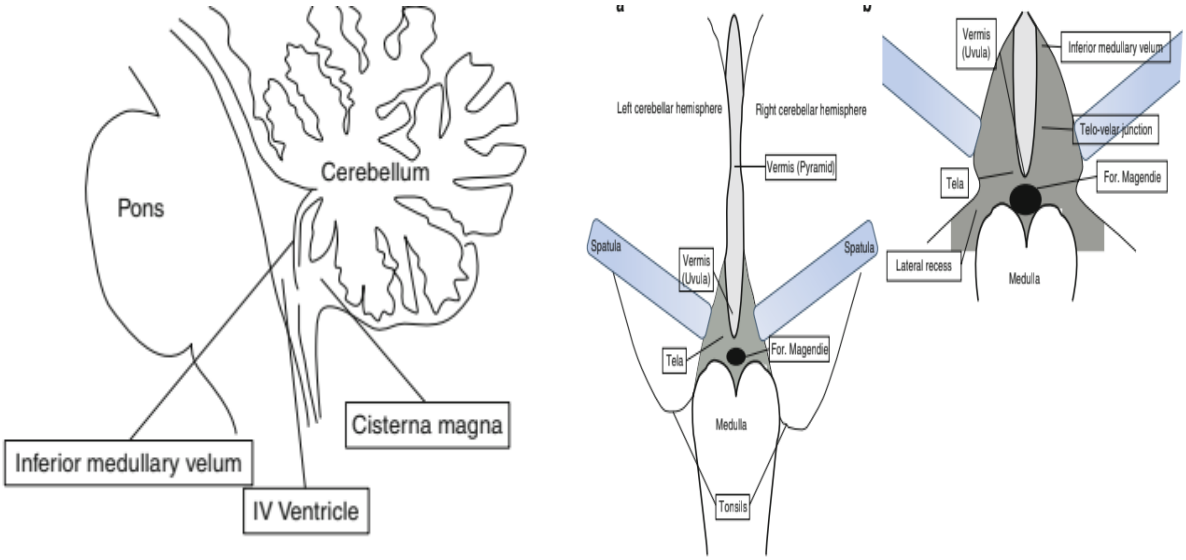


Figure 16:

Schematic drawing of the inferior medullary velum and its relationship with the fourth ventricle and cisterna magna

Schematic drawing of the tela choroidea (a) and inferior medullary velum (b) , following spatulation of the cerebellar tonsils

Sagittal MRI can help delineate relationship of the tumor to the vermis, midbrain tectum, vein of Galen, and cervicomedullary junction and distinguish between true intraventricular tumor such as medulloblastomas that dislocate postero-superiorly the superior medullary velum and the quadrigeminal plate and widen the aqueduct from vermian in which the quadrigeminal plate is dislocated anterior-inferiorly (**Figure 17)** . Because of high frequency of craniospinal metastasis, even at presentation, all the neuraxis should be mandatorily scanned before surgery.

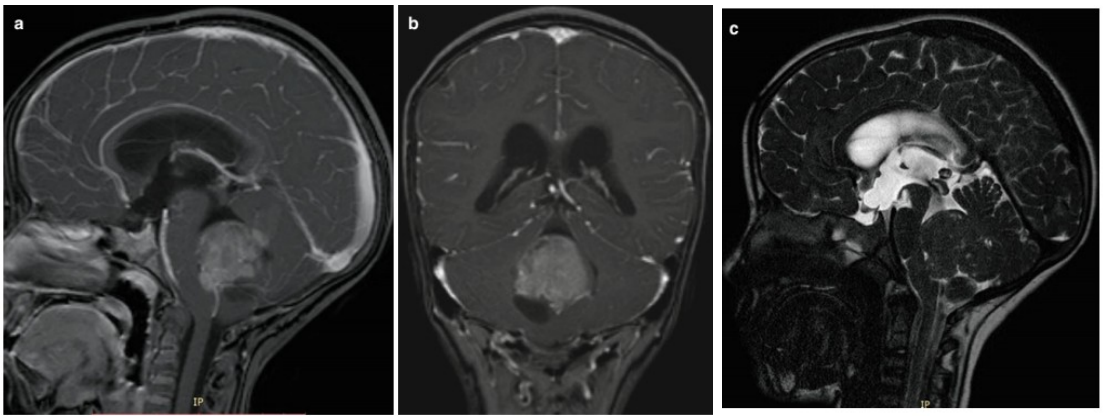


Figure 17 Typical medulloblastoma arising from the inferior medullary velum, filling the fourth ventricle. Sagittal and coronal contrast-enhanced T1 WI images (a, b); Midsagittal DRIVE sequence (c)

Operative Technique

Positioning

The prone position is preferred for all midline posterior fossa approaches. It has advantages like :

- Decreased risk of air embolism and the absence of postoperative pneumocephalus that is a constant finding following posterior fossa surgery in the sitting position.
- Moreover the surgeon works more comfortably, and there is less risk of tearing bridging veins between the cerebellum and tentorium than in the seated position.

In older children the head can be fixed in a rigid pin-type head holder.

Flexion of the neck with reverse Trendelenburg positioning of the torso is very important because it allows for visualization of the rostral part of the posterior fossa, i.e., tentorium, pineal region, and cerebral aqueduct.

Venous drainage is improved as like dissection of the occipitocervical musculature. Care should be taken to avoid over flexion: it may be dangerous in case of tonsillar herniation through the foramen magnum, and may prevent adequate venous drainage through neck veins.

The iliac crests are supported with bolster; the abdomen is left free to avoid venous engorgement.

The shoulders should be supported with adequate padded pillows to slightly project beyond the operating table, so that flexion of the neck will not place the endotracheal tube close to the table.

In obese children silk tape should be used to pull the shoulders caudally and place the occipitocervical musculature under tension. All pressure points should be padded.

Surgical Approach.

- ✓ A midline incision from the inion to C2 is traced.
- ✓ The dissection is taken through the avascular midline. Unless imaging studies suggest tumor extending caudally beyond C1, one should avoid taking the paraspinous muscles off the laminae of C2 contributing to postoperative pain and a risk of postoperative cervical instability.
- ✓ A craniotomy or craniectomy can be used for posterior fossa approaches. Two paramedian burr holes are drilled just below the lateral sinuses, on either side of the midline to exactly locate it and the torcula.
- ✓ With the help of rongeurs, craniectomy is completed at the level of the foramen magnum. If imaging studies reveal tumor below the level of the obex or tonsils caudally displaced, the posterior arch of C1 should also be removed, with the help of rongeurs.

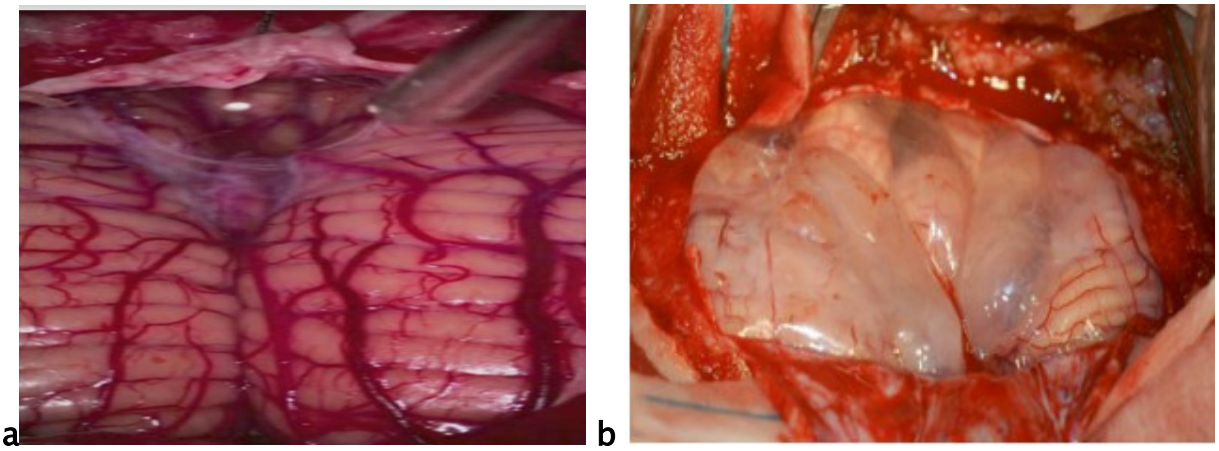
- ✓ Dura mater is opened in a Y shape, with the base along the lateral sinuses and midline durotomy extended caudally. Bleedings from the dura and occipital sinus should be controlled with dural clip or circumferential sutures. Every effort should be done to avoid mono or bipolar cautery on the dura. The dural flap should be retracted upward with sutures to expose as much cerebellum as possible.
- ✓ The retracted dura should be left retracted upward and laterally by retracting sutures, protected with a wet patty between the dura and the bone and a second wet patty above the dura.
- ✓ If a "Y" incision is done, two additional retracting sutures should be placed in the two points joining the cervical dura incision with the cerebellar dura incision.
- ✓ Two additional long wet patties should be placed vertically under the cervical dura and under the retracting sutures, allowing to keep the cervical dura wet and avoiding blood to enter the surgical field from the extradural space at the level of the occipital foramen. Frequent moistening of these patties should be ensured.
- ✓ Absolute, perfect hemostasis of the extradural space and a perfectly clean operative field should be obtained before starting microsurgical dissection.

Microsurgical Dissection.

For medulloblastomas located into the fourth ventricle, microsurgical dissection begins with;

- o Opening the cistern magna (**Figure 18.a**). This helps in relaxing the brain, releasing CSF. Many surgeons sample the CSF from cistern magna to determine if there are malignant cells on cytology (**Figure18.b**) [**72].**

- Usually the tumor grows underneath the vermis, progressively filling the fourth ventricle and underneath between the cerebellar tonsils: initial exposure may be facilitated by splitting the tonsils if the tumor has not already done so (**Figure 19**).
- The initial goal of dissection is to find and protect the floor of the fourth ventricle. If the tumor is not adherent at the level of the obex, microsurgical dissection of the arachnoid about the vermian peg will allow for elevation of the inferior pole of the tumor and visualization of the distal fl oor (**Figure 20**).



a b

Figure 18.a microsurgical dissection of the cisterna magna

Figure18.b.Cisterna magna filled by several small tumoral nodules

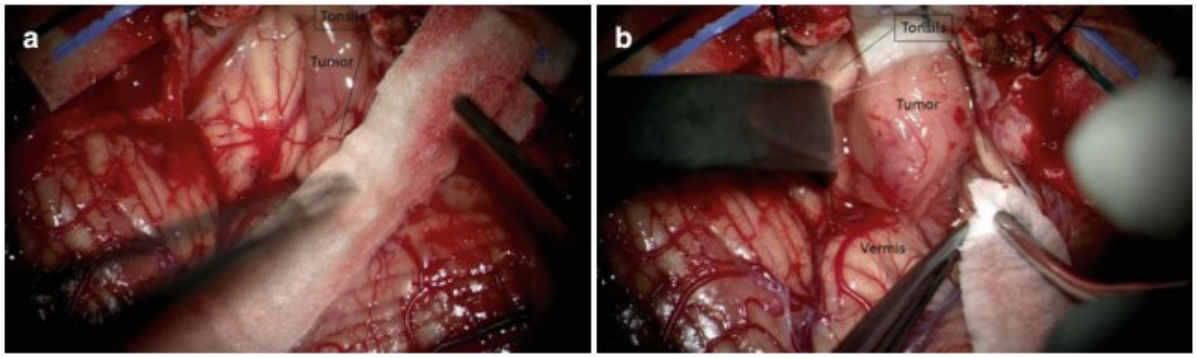


Figure 19 The tumor is visible in the cisterna magna. The tonsils are gently divided following incision at the arachnoid (a). Further dissection of the tumor from the cerebellar tonsils and inferior vermis allows better exposure of the tumor (b)

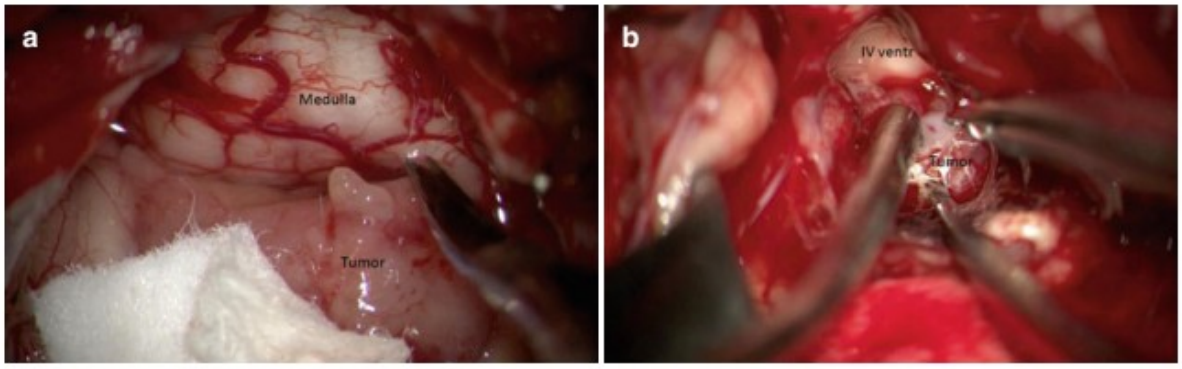


Figure 20 The inferior pole of the tumor is dissected from the medulla at the level of the obex (a). Following dissection the inferior pole of the tumor is removed to expose the distal fl oor of the fourth ventricle (b).

The two most common surgical routes to expose medulloblastoma in the fourth ventricle are the transvermian and telovelar approaches.

This involves dividing the inferior vermis of the cerebellum and retracting the two halves of the vermis in opposite lateral directions.

In the second approach, the tela choroidea and inferior medullary velum are opened, and the lower vermis is retracted superiorly **[73]**.

Sometimes the two techniques can be fused

6.2.1. Telovelar Approach.

The telovelar approach is the preferred approach for all fourth ventricular tumors: medulloblastoma, protruding through the foramen of Magendie and stretching the tela choroidea and inferior medullary velum over its surface, is usually the ideal candidate for this approach. Recently has been underlined that using the telovelar approach in very large and giant tumors may be hazardous.

- By opening of the cisterna magna and lifting of the tonsils off the brain stem it exposes the intertonsillar space so that the tonsillomedullary part of the cerebellomedullary cleft is exposed.

- Following this, the foramen of Magendie is exposed and is enlarged by cutting the tenia along the inferior cerebellar peduncles till the lateral recess.
- Dissection is extended between the medial side of the tonsils and the adjacent edges of the uvula (uvulotonsillar cleft). Special attention is directed to the location and bifurcation of the PICA into medial and lateral trunks. Care should be taken to protect it.
- Complete dissection of this cleft will expose the inferior medullary velum, the incision of which will expose the superior and superolateral part of the fourth ventricle

The telovelar incision can be divided in three parts.

3.2. The first part of the incision, which opens the tela choroidea, begins inferiorly near the foramen of Magendie in the lower portion of the ventricle roof and extends upward to the level of the junction of the tela with the inferior medullary velum. In most cases, this is suffi cient to expose the full length of the fl oor of the fourth ventricle.

3.3. The second part involves extending the incision superiorly through the inferior medullary velum, which is exposed in the depths of the uvulotonsillar space. The vein of the cerebellomedullary fissure, which crosses the inferior medullary velum, can be transected in some cases. Incising the inferior medullary velum on one uvulotonsillar space exposes the ipsilateral superolateral recess and provides access to the entire fl oor of the fourth ventricle. Shifting the exposure to the opposite uvulotonsillar space and opening the tela and velum provide an identical exposure on the other side **[73].**

3.4. The third incision can be directed between the tonsil and medulla oblongata through the tela forming the lower posterior wall of the lateral recess: it provides additional access to the full length of the lateral recess and the foramen of Luschka.

6.2.2. Transvermian Approach

The transvermian approach is the oldest and most widely used. It consists of splitting the inferior vermis on the suboccipital surface, with variable extension depending on the location and size of the tumor. Most authors advocate limiting the vermian incision to the smallest possible length necessary to gain access to avoid complications.

- The midline incision of the inferior vermis is extended to the tela choroidea and inferior medullary velum: the full length of the floor (mean length 4 cm) from the aqueduct to obex can be exposed through this approach **[73].**
- Adequate lateral exposure including the lateral recesses and both foramen of Luschka can be obtained combining the cerebellar retraction that should be as delicate and limited as possible, with the use of the full range of lateral bending of the operative microscope. This allows to put the whole volume of the fourth ventricle cavity in a line of sight adequate for less invasive surgery. Further help both for the upper part and for the lateral recesses of the fourth ventricle can be offered by the intraoperative use of the endoscope.

As discussed in the study of Tanriover et al. **[73],** both the transvermian and telovelar approaches provide excellent exposure of the entire fourth ventricle. The telovelar approach provides additional access to the lateral recesses and foramen of Luschka. The transvermian approach provides a slightly better exposure of the

midline superior half of the roof of the fourth ventricle and fastigium. However the article by Deshmukh et al. [74] emphasizes that this unique advantage of the transvermian approach is by C1 laminotomy when added to the telovelar approach.

The transvermian approach requires an incision into the cortical and functional areas of the cerebellum with well known disadvantages including:

- The splitting of the inferior cerebellar vermis may cause caudal vermis syndrome, resulting in an equilibratory disturbance with truncal ataxia, gait disturbance, oscillation of the head and trunk, and nystagmus.
- Also dentate nucleus, being located along the posterolateral margin of the roof of the fourth ventricle, is at risk.
- Lesions of the caudate nucleus may be responsible of more severe equilibratory disturbances often accompanied by intentional tremor during voluntary movement of the extremities [76].
- Splitting the inferior portion of the vermis may also play a role in cerebellar mutism.

Tips and tricks.

i. The anatomy is severely distorted and dissection in the uvulotonsillar cleft before decompression can result in breaching the pial plane and entering either vermis or tonsil leading to neurological deficit.
ii. Placing the retractor on the superomedial part of the tonsil can injure the dentate nucleus and damage to veins and arteries can occur leading to ischemic injury to the vermis and deep cerebellar nuclei [75]. Such problems can be overcome by doing dissection and decompression simultaneously.

iii. Initial decompression followed by dissection of the planes of the telovelar approach will help in minimizing retraction and reducing retraction-induced injuries [75].

iv. The tumor is dissected from surrounding cerebellar and brainstem structures using microsurgical techniques. Usually circumferential dissection of medulloblastomas is precluded by their size; thereafter debulking should proceed simultaneously with dissection also at this stage. Medulloblastomas have usually soft consistency; thereafter debulking may be done with either suction or ultrasonic aspirator.

v. The surgeon should allow the tumor to deliver itself into the aspirator. Portions of the tumor not adherent to the floor of the fourth ventricle will deliver themselves, exposing the white floor, and rostrally the aqueduct with small cotton patty placed over the aqueduct to prevent blood from entering the ventricular system.

vi. No forceful dissection should be attempted for medulloblastomas invading the floor of the fourth ventricle or the aqueduct.

vii. Once exposed the entire floor, dissection should proceed laterally to define a plane between the tumor and cerebellar hemispheres. Distinction between tumor and cerebellar white matter is usually clarified with high magnification. Great attention should be done to remove the tumor from the lateral recesses.

viii. Before closing, the walls of the resection cavity should be checked carefully for residual pathological tissue.

ix. Adequate hemostasis is verified with a Valsalva maneuver and the surgical bed copiously irrigated with warm saline.

x. Attempts should be made to obtain hemostasis avoiding leaving behind hemostatic agents that may migrate and obstruct CSF pathways and will cause artifact on postoperative imaging.

For non-midline medulloblastomas a suboccipital approach, with bilateral dura opening, even if the tumor is entirely in a single hemisphere.

Bone and dura openings are more extended towards the side of tumor. Bilateral exposure and dural reduces the risk of cerebellar swelling during opening.

If the tumor is not visualized on the cortical surface, it can be located and the direction of dissection planned with intraoperative ultrasound.

Hemispheric tumors are approached in the most direct manner through the thinnest portion of the cerebellar cortex via a horizontal incision.

Medulloblastomas may also present as cerebellopontine angle tumors. These tumors can be operated via a standard suboccipital retromastoid approach. Usually the approach should be extended to expose the transverse and sigmoid sinuses on the affected side.

Considering the efficacy of the adjuvant treatment, microsurgically complete resection should only be intended in case of tolerable risk. In case of significant residual tumor, particularly in nonmetastatic disease, second- look surgery should be discussed.

Treatment of relapsing medulloblastoma depends on several factors. The role of surgery is usually limited. In older children who have already received craniospinal radiation as part of their initial therapy, surgery may be an option for solitary recurrences. However, prognosis following relapse is poor with less than 5 % long-term survivors.

7. Complications

Some complications related to surgery include.

- Intraoperative hemorrhage is a rare complication of medulloblastoma surgery. It presents as massive cerebellar swelling, following dural opening that is related with ligation of the occipital sinus. Ligation of the occipital sinus may disturb the venous drainage and elevate the venous pressure. To avoid this preoperative MRI venography should be obtained and posterior fossa dura should be opened without interruption of the sinus drainage.
- Postoperative hydrocephalus.
- Hematoma.
- Aseptic meningitis.
- Cervical instability.
- Neurological deficits secondary to damage of the cerebellum, brain stem and cranial nerves.
- Cerebellum is also involved in higher cognitive processes: damage to the dentate nuclei, the vermis, and the right cerebellar hemisphere result in significant reductions of intelligence quotient (IQ), with adverse neuropsychological outcomes.
- Cerebellar mutism. This term refers to muteness that follows lesions of the cerebellum. Its unique features are delayed onset (1–6 days) and limited duration (1 day–4 months). Its incidence after posterior fossa surgery in children is 11–29 %. Recovery is spontaneous but not always complete. Risk factors include brainstem involvement and midline location. These

factors render medulloblastoma the most likely posterior fossa tumor to cause cerebellar mutism following surgery.

METHODOLOGY

II. METHODOLOGY.

From 2016 to 2019 we retrieved 34 patients. These patients had surgery and were all operated with histopathology confirming the diagnosis of medulloblastoma.

Inclusion criteria included

- All patients who were treated in our department from diagnosis to surgery and adjuvant therapy.

Exclusion critera included

- Patients retrieved with insufficient data for the study.

Our study had a number of general and specific objectives.

GENERAL OBJECTIVE

- To describe the day to day management of patients in our hospital suffering from medulloblastoma

SPECIFIC OBJECTIVES

- ❖ Describe the demographic and clinical profiles of patients with medulloblastoma
- ❖ To describe the surgical procedure of these patients
- ❖ To give a detailed histopathology report of patients
- ❖ To describe the adjuvant therapy of patients
- ❖ To describe the complications encountered
- ❖ To give conclusions and recommend dations of our study.

We carried out a retrospective study from January 2016 to 2019. The study was carried out in the department of neurosurgery in collaboration with the department of histopathology medical oncology and radiotherapy.

The procedure included a clinical survey, histopathology, radiotherapy and medical oncology.

We established a pre formed questionnaire that included informations concerning the clinical profile of patients, the histologic profile and the protocol for chemotherapy and radiotherapy.

Clinical profile included the demographic profile of patients, the signs and symptoms the patient presented. Under this aspect we also studied the radiological presentations of medulloblastoma.

Results from the anatomopathology laboratory were noted and we considered the histologic subtype and the molecular subgroups if it was presented.

We worked with the medical oncology and radiotherapy units. We followed their treatments option with respect to age and followed the evolution of the patient after initiation of adjuvant therapy.

Follow included the clinical status as well as craniospinal MRI to find out any sign of metastasis.

We analysed the treatment options from shunting to tumor resection specifying the route of the surgical procedure and the extent of surgical resection. We also explored the complications related to surgery and to the tumor.

Generally a piece of tumor was sent for analysis. The laboratory of the University teaching hospital of Fez. Analysis was done to classify the histologic type of medulloblastoma.

We also studied different protocols issued to patients following surgery either by chemotherapy or radiotherapy.

These were done using pre formed questionnaires that incorporated the clinical surveys, data collection for radiological images and adjuvant therapy protocols.

Collected data was computed and validated using EPI INFO software. All entries were further cheked on paper; item by item so as to ensure accuracy of the

data entered. The data were exported to the Microsoft Excel 2003 and Stastistical Package for Social Software, SPSS compatible file for furthrer analysis.

RESULTS

III. RESULTS.

Thirty four patients fufilled the inclusion criteria.

1. Characteristics of the study population and distribution of the population by age and sex

Of the 34 patients 12 (35 percent) were females and 22 (65 percent) zere males. The age range was from 1-61 years with a mean age of 16 years old. We distributed the population study in different age groups.

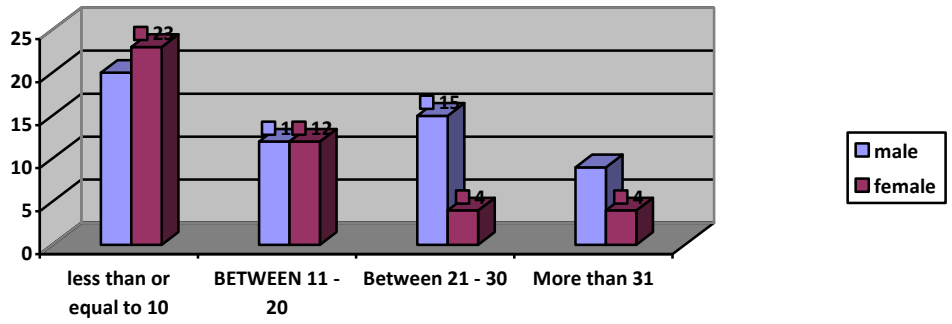


Figure 21: Distribution of the study population by age and sex.

The study population was represented by those less than equal to 10 years old representing 44% of the study population with the least age group represented by tose above the age of 30. We also note an evenly distribution of the patients between 11 and 20 years old.

2. Clinical manifestations of medulloblastoma.

All the patients retrieved presented with cerebellar symptoms and signs of raised intracranial pressure.

Cerebellar syptoms included either static or dynamic symtoms. Signs of raised intracranial pressure was present in all our patients; this varied from headache, vomitus and papilloedema of different intensity.

2.1. Cranial palsy.

12 patients (36%) out of the 34 retrieved presented with cranial palsy. Among the 12 patients we noted that all presented with VI nerve paralysis. Four among the 12 presented with paralysis of the mixed nerves with difficulties in swallowing.

3. IMAGING.

All our patients had a computed tomography (CT) scan prior to a magnetic resonance imaging (MRI). A CT scan was always the first neuroimaging at presentation of symptoms. The exploration was later continued by a cerebral MRI. All of these presentations were in the posterior fossa.

3.1. CT SCAN IMAGING CHARACTERISTICS.

Twenty five (74%) out of the 34 retrieved presented with isodense presentation on unenhanced CT scan; seven (21%) showed slightly hyperdense images and three patients (5%) showed a slightly hypodense imaging heterogenous we mean images of hypodensity and hyperdensity. Hypodense presentation were usually associated with cystic components of the tumor.

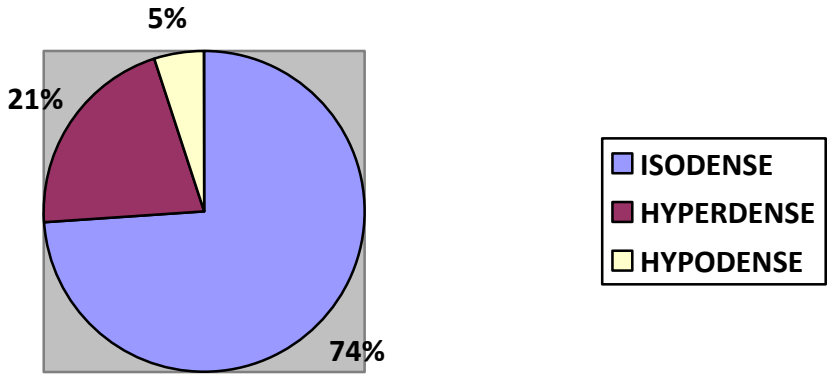


Figure 22: distribution of image density on CT scan.

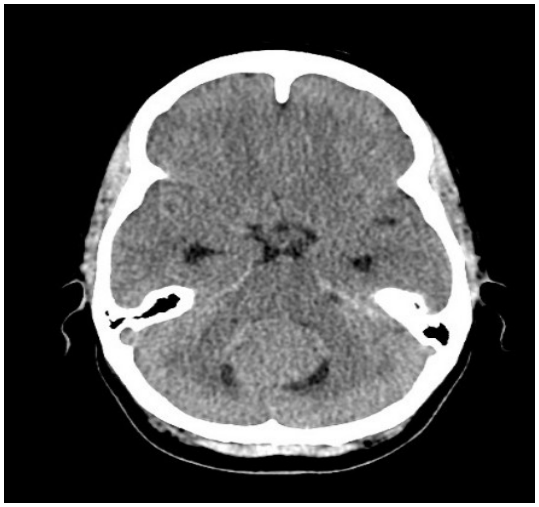
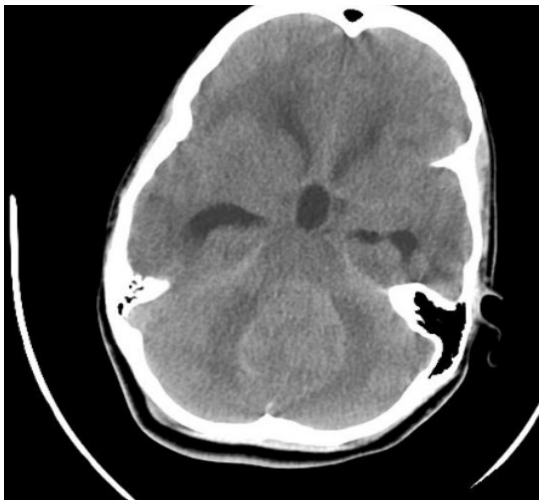
(i)  (ii) 

FIGURE 23 : isodense presentation of the tumor note perilesional oedema present on image ii

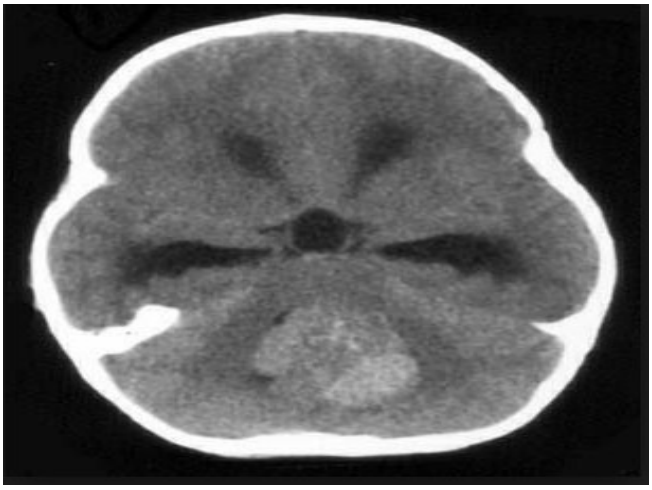


Figure 24: unenhanced CT scan image showing a slightly hyperdense image of medulloblastoma.

The head CT scan also presented images of intratumoral calcifications present. Calcifications were present in 10 of our 34 patients retrieved.

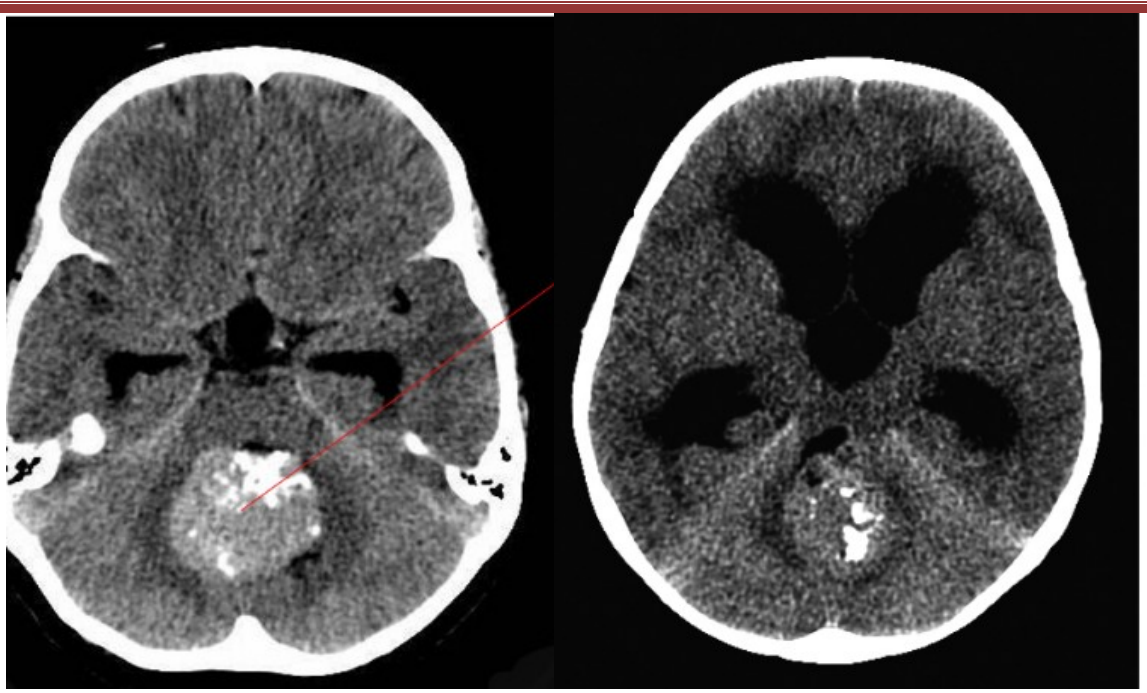


Figure 25: shows on unenhanced CT scan image intratumoral calcifications present.

CT SCAN ENHANCED IMAGE

All of the presentations showed enhanced images on the head CT scan. Enhancement were of varied degrees.

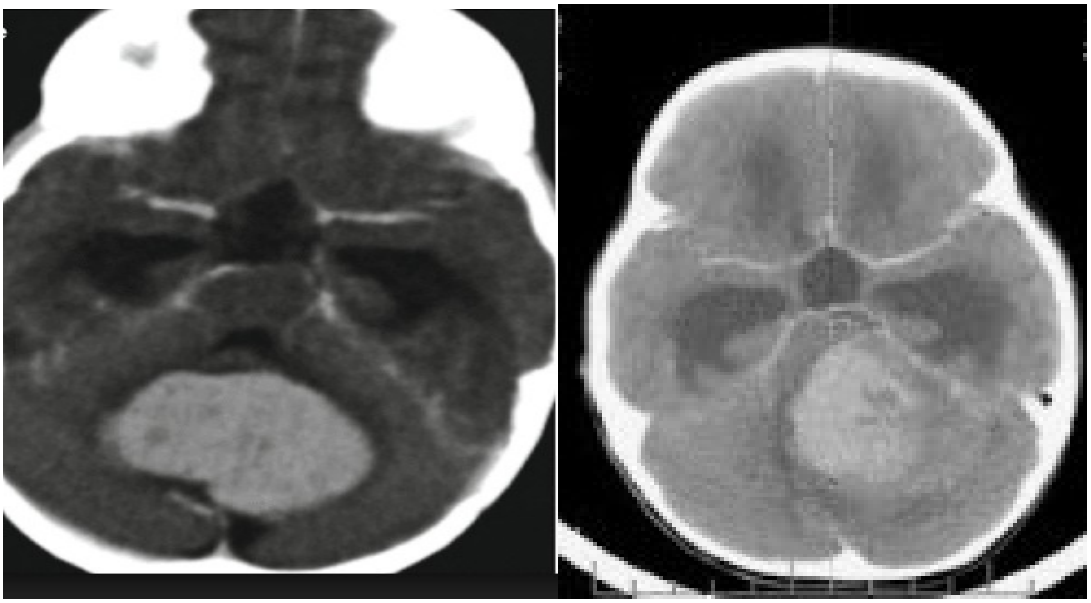


Figure 26: All of the patients retrieved presented with hyrdocephalus with either dilation of the third ventricle or the dilation of the temporal horn of the lateral ventricles.

3.2. MRI PRESENTATION.

All our patienTs retrieved had a head MRI done. All sequences zere carried out during.

3.3. TUMOR LOCALISATION.

All tumors were located in the posterior fossa. Localization were in majority vermian and six among them were cerebello-vermian and to patients presented atypical presentation of cerebellar localization.

TUMOR LOCALISATION	NUMBER
VERMIAN	26
CEREBELLO-VERMIAN	6
CEREBELLAR	2

In majority the tumors presented characteristics of malignant that is they presented hypointense on T1 and enhanced highly after administration of gadolinium with images of hyperintensity on FLAIR showing images of oedema.

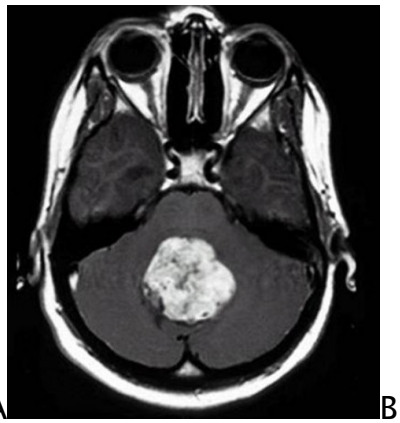
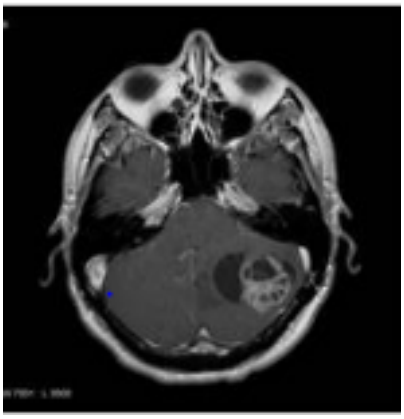
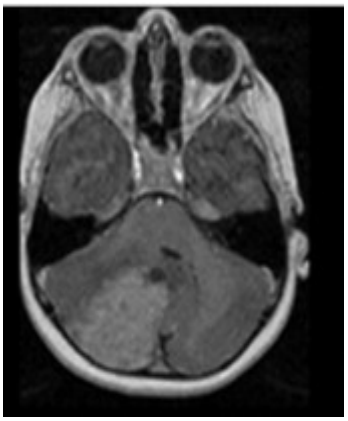
A  B  C 

Figure 26: Images showing different locations of tumors in our study. The majority of these tumors zere vermian with either partial or complete obliterartion of the the fourth ventricle.

B; showing one of the two tumors that presented a cerebellar location.

C; cerebello vermian presentation of medulloblastoma.

3.4. TUMOR SIZE

Of all patients retrieved, the tumors had a minimum size of at least 4cm with maximum sizes of 6cm. During our study we recorded a mean siwe of 5,5cm.

All patients retrieved had also extra cranial imaging in search of metastatic location of medulloblastomas. We performed a cerebro-spinal MRI imaging in search of secondary locations.

Of the 34 patients retrieved, 3 patients presented metastasis.

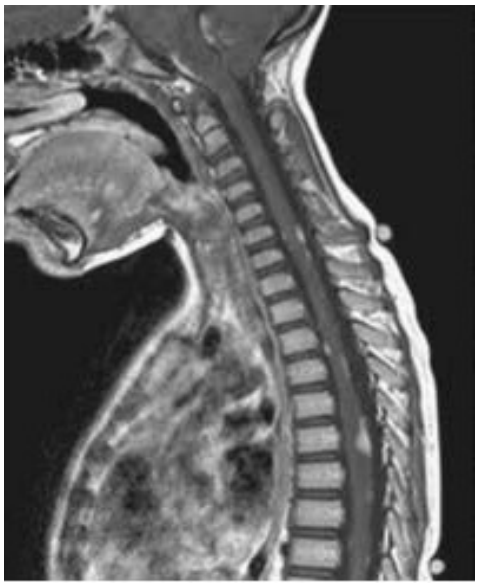


Figure 27 : Showing spinal metastasis of medulloblastoma at multiple levels.

4. MANAGEMENT.

4.1. SHUNTING.

Twenty eight patients had shunting before surgery. The remaining six patients had resection tumor surgery without having undergone shunting.

Among the 28 patients who had shunting, 19 of them had ventriculocisternostomy meanwhile 9 patients had a ventriculoperitoneal shunt.

SHUNTING.		NO SHUNTING
28		6
Ventriculocisternostomy	Ventriculoperitoneal Shunt.	
19 (68%)	9 (32%)	

4.2. Surgery

All 34 patients had surgery with objective of tumor resection. The average time lapse for tumor resection was 56 days. However these patients received an emergent shunting before planning for surgery. The mode of surgery was either through transvermian and telovelar approaches.

In our department, indications for each approaches depends on

- Surgeon's preference.
- For midline tumors we generally prefere a transvermian approach while for cerebello-vermian tumors we go for a telovelar approach.

Twenty-eight patients had transvermian approach meanwhile 6 patients had the telovelar approach of surgery.

For both approaches head positioning is similar involving a patient on ventral decubitus with hyperflexion of the head.

- All patients are operated in prone position.
- The skin incision is mid line from just above the union to the spinous process of the atlas.
- Removal of the C1 posterior arc id done so as to have a good control of the foramen magnum.
- The standard suboccipital craniectomy extend from the inferior edge of the transverse sinus to and including the posterior rim of the foramen magnum which is adherent to the dura and should be cautiously dissect.

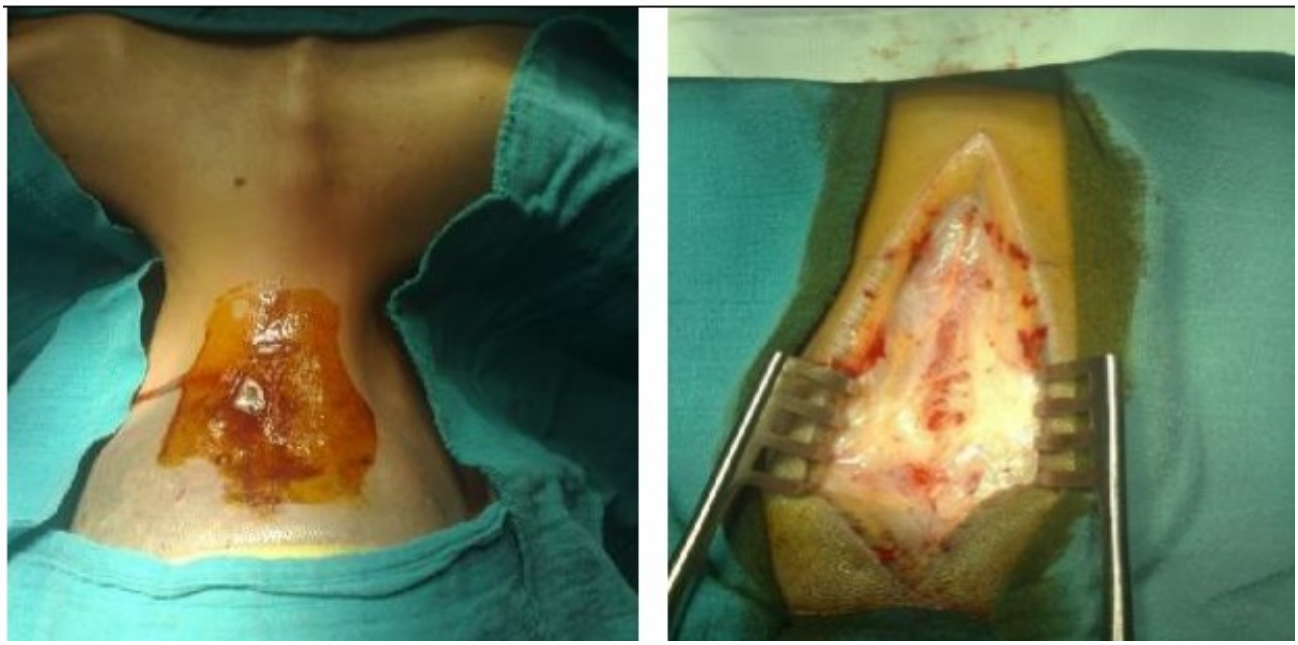


Figure 29: prone position and incision of the skin from the inion to the C2 spinous process.

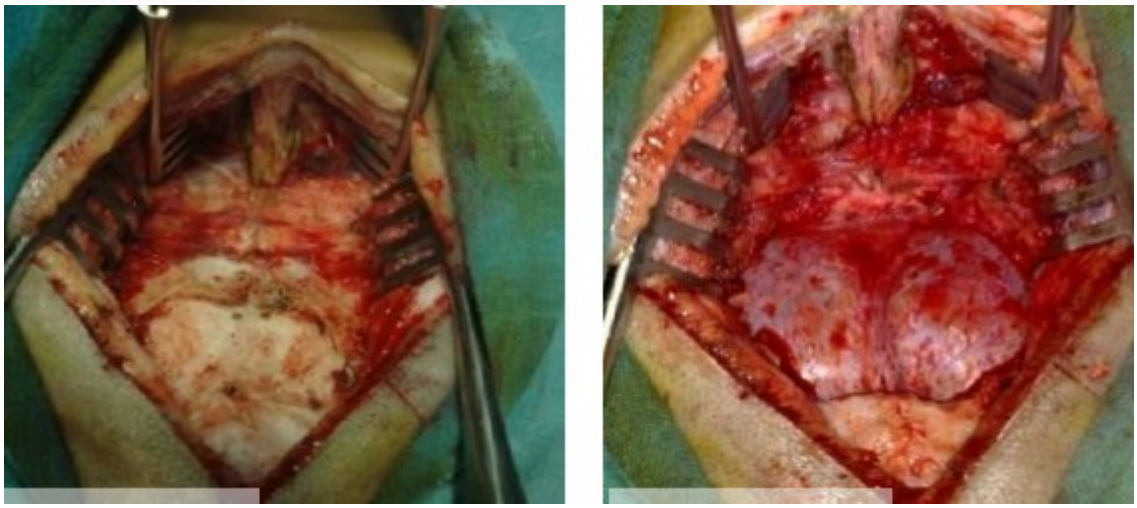


Figure 30 : showing complete muscle dissection and exposure of the occipital bone. Other image showing occipital craniectomy.

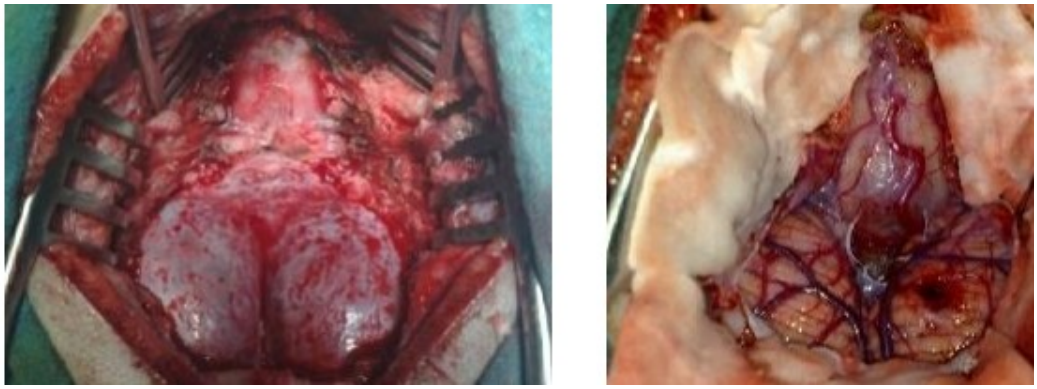


Figure 31 : Dura mater exposed and opening of the dura.

4.2.1. TRANVERMIAN APPROACH.

The transvermian approach involves separating both cerebellar hemispheres and exposing the vermis.

In our department after appropriate exposure and opening of the dura with the aid of the operating microscope we then

- Split the inferior vermis on the sub-occipital surface. The incision extends a variable distance through the uvula, pyramid, tuber, and folium of the vermis, depending on the location and size of the lesion. Generally

we do not exceed more than 15mm of splitting so as to avoid post operative complications of cerebellar mutism.

- Retracting the two halves of the lower vermis laterally, then opening the telachoroidea and the inferior medullary velum, exposing the full length of the floor from the aqueduct to the obex.
- Tumor resection is done by gradual debulking, suctioning and cauterizing.
- After considerable debulking we then mobilise the tumor more easily. As this is done we use cottonoids to delineate the tumor borders and separating it with the brain parenchyma.
- As we liberate the fourth ventricle from the tumor we usually place a piece of cottonoid in the aqueduct of sylvius this is to avoid blood in the ventricles and a possible hydrocephalus.

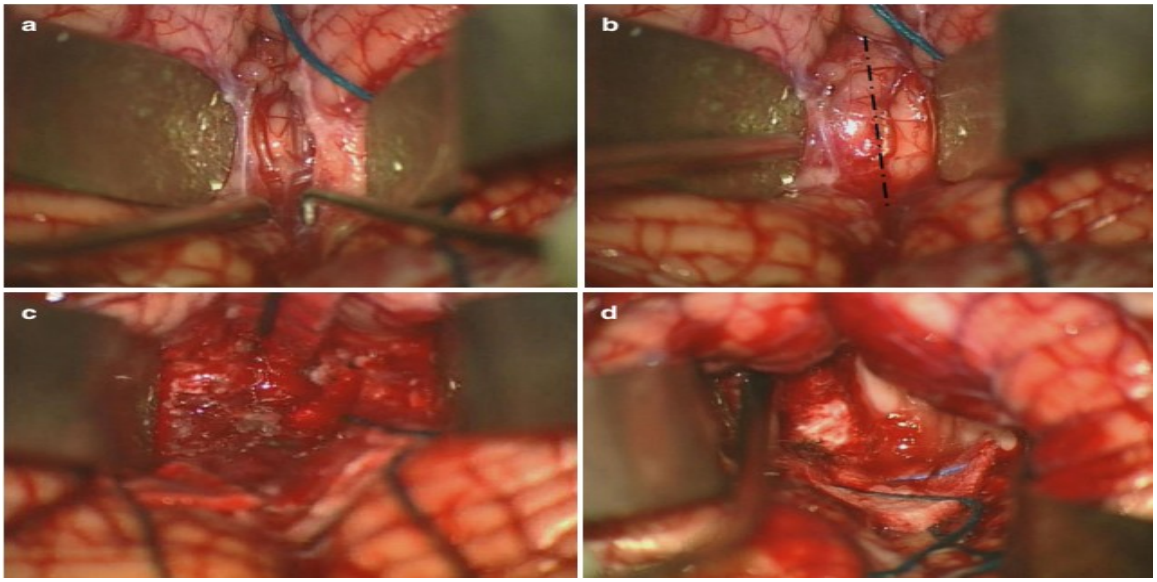


Figure 32 Transvermian approach:

arachnoid between the two cerebellar hemispheres is incised, (a) the two hemispheres are dissected away from the midline, and the inferior vermis is exposed (b dotted line : line of incision) The tumor is found few millimeters below the incision of the vermis and is debulked (c) Finally the fourth ventricle floor is exposed (d)

4.2.2. Telovelar approach.

This approach is less practiced in our department. Major indications include a cerebello-vermian localization of the tumor. This technique is thus as follows

After adequate exposure and complete opening of the dura mater, the technique consists in

- The medullotonsillar space of the cerebellomedullary fissure and the uvulotonsillar space are sharply dissected to release the tonsils from the uvula and the medulla oblongata bilaterally.
- The two cerebellar tonsils are then retracted laterally to expose the floor of the fissure. The telachoroidea is incised from the foramen of the magendie and then followed laterally to the foramen of the luschka on both sides.
- Opening both sides gives a large exposure of the fourth ventricle that is filled with the tumor. The advantage is that for laterally extending tumors this approach offers accesibilty to the lateral recess.

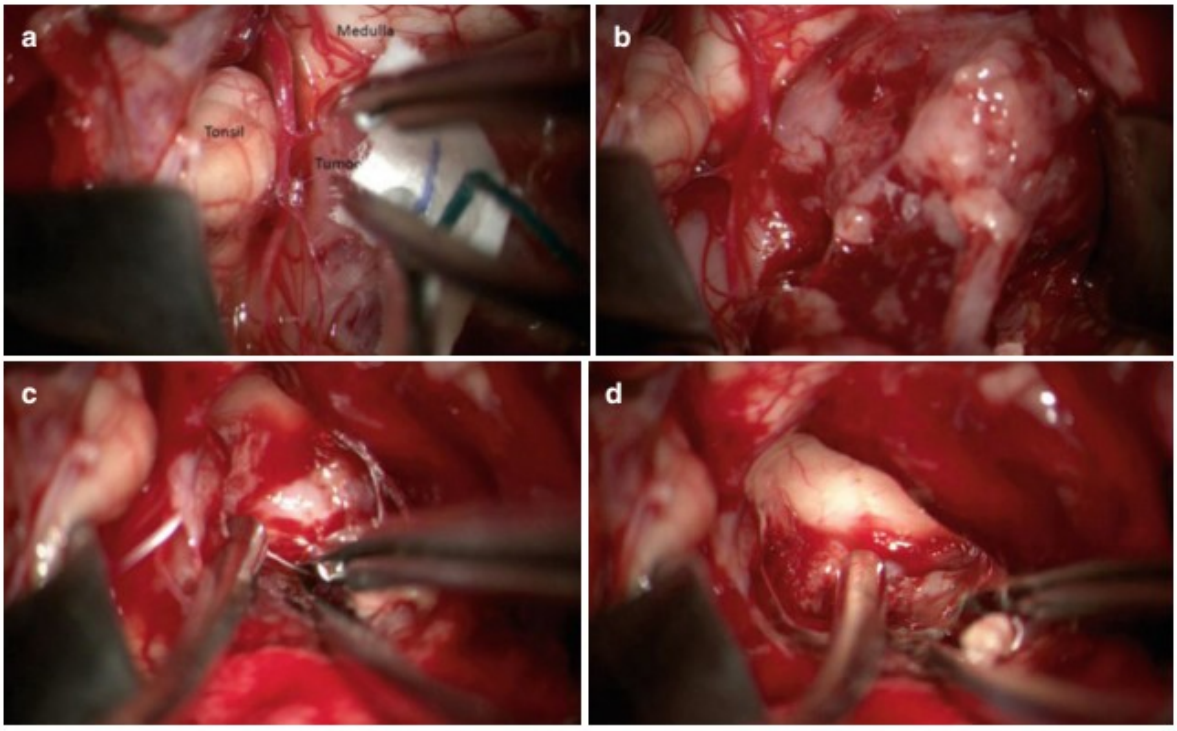


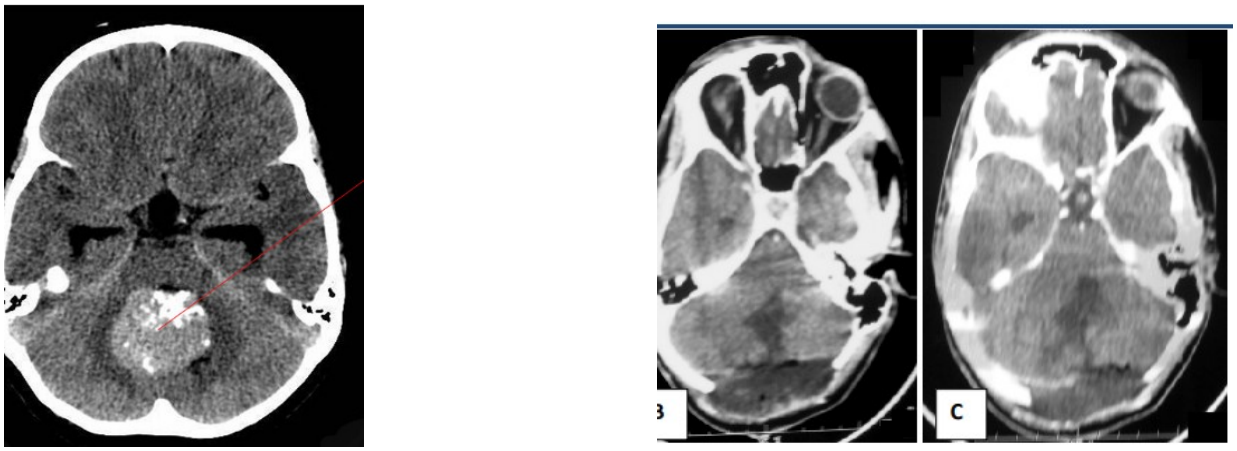
Figure 33 Tumor is dissected laterally from the tonsil to expose the telovelar junction (a). The dissection is alternated with debulking (b, c), until the fl oor is exposed (d).

Following surgery, we noted a total tumor resectioin among 19 patients and the remaining had sub total resection. Total resection was noted intraoperatively and on post operative images. Usually our post operative images include CT scans. In general sub total resection is due to the invasiveness of neural structures by the tumor. Among the patients retrieved in terms of subtotal resections few millimetres was left.

5. TIME LAPSE BEFORE TUMOR RESECTION.

An average of 53 days was the time lapse from diagnosis to tumor resection. During this period patients generally have an intermediate surgery to relieve patients from raised intracranial pressure either through ventriculoperitoneal shunts or ventriculosisternostomy.

Surgical resection was total in some cases and in other cases this was a sub total resection



Before surgery After surgery (complete resection)

Figure 34: showing resection complete with post operative CT scans.

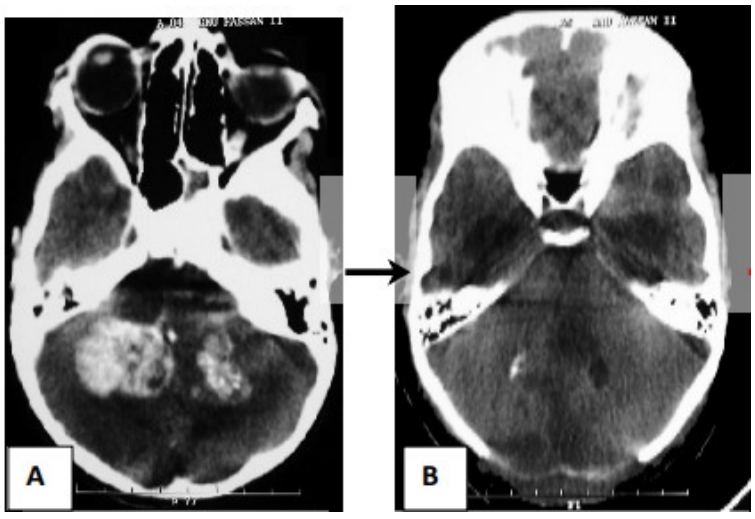


Figure 35: showing a sub total resection of the tumor by showing a contrast image after surgery.

6. HISTOLOGICAL FINDINGS.

Our patients benefited from a histologic subgroup classification. Of the 3 patients retrieved, the distribution was as follows. In our study half of our patients did not have a specified histologic subtype stated. However for the remaining half, most of the patients suffered showed in majority the desmoplastic form and a smaller proportion of classic medulloblastoma. Our study did not register large cell nor anaplastic histologic subtypes.

Histologic subtype	Proportion.	Ages
Desmoplastic	14 (41.2%)	7 patients less than 3 years old 4 patients above 3 years but less than 10 3 patients between 11 - 20 years old
Classic	3 (8.8%	All 3 between 4 – 10 years old.
Large cell	Non	-
Anaplasic	None	-
Non identified histology	17 (50%)	All were distributed in every population group study.

7. COMPLICATIONS.

We noted a number of complications following surgery.

i. Cerebrospinal leakage

This was the most encountered among post operative complications. Twenty patients (20) presented CSF leak in our study. Amon the 20, five were patients who did not receive shunting before surgery and the 15 other patients shozed leakage after the dura was not closed in a water tight manner.

To correct this, patients were shunted and others had consecutive lumbar taps and in case this was unsuccessful, patients were operated again for adequate closure of the dura mater.

ii. Wound infection and meningitis

Postoperative infections range from superficial wound infection to deep infections that involve the bone flap or meninges Meningitis was diagnosed at least 5 days following surgery and the causal germs were bacterias. In our study germs that were retrieved zere generally *staphylococcus sp*, *meningococcus sp.*

Treatment options included antibiotics associating vancomycine, third generation cephalosporines and aminosides.

iii.Intracranial suppurations.

Cerebral abcess and subdural empyema was noted among 10 patients during our study. This was diagnosed after a paersistent inflammatory syndrome. All patients were operated for surgical excision and thorough lavage.

Among the 10 operated 2 had a positive pus culture identifying *staphylococcus sp.* They received antibiotics adapted to germs after an antibiogram was done. For the rest of 8 patients, cultures were sterile and patients received an association of three antibiotics including vancomycine, third generation

cephalosporines (ceftriaxone or ceftazidime) and metronidazole. Doses were always given in meningeal doses.

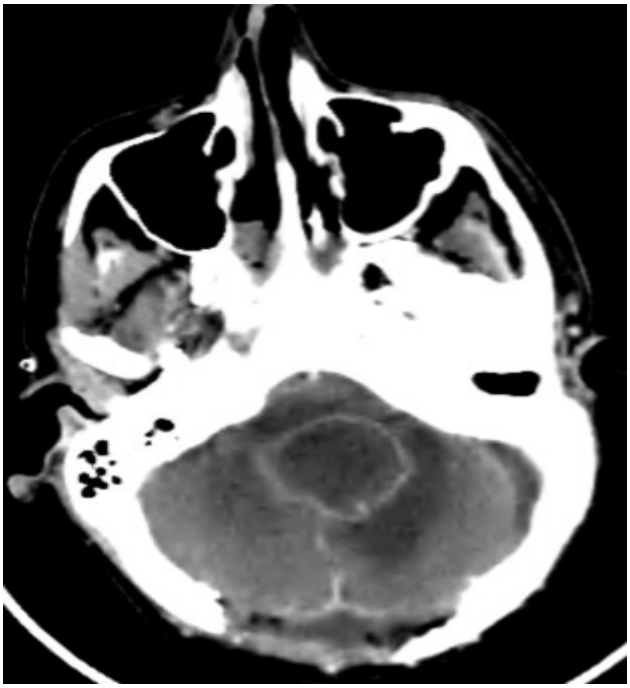


Figure 36:Post operative image of a cerebellar abcess following resection of medullobalstoma

iv. <u>Infarction on the vascular territory of the basilar artery.</u>

This complication was encountered on one patient who failed to wake up on post op and a control CT scan showed ischemia of the posterior fossa. A CT angiogram shozed the origin from the basilar artery and the antero inferior cerebellar artery.

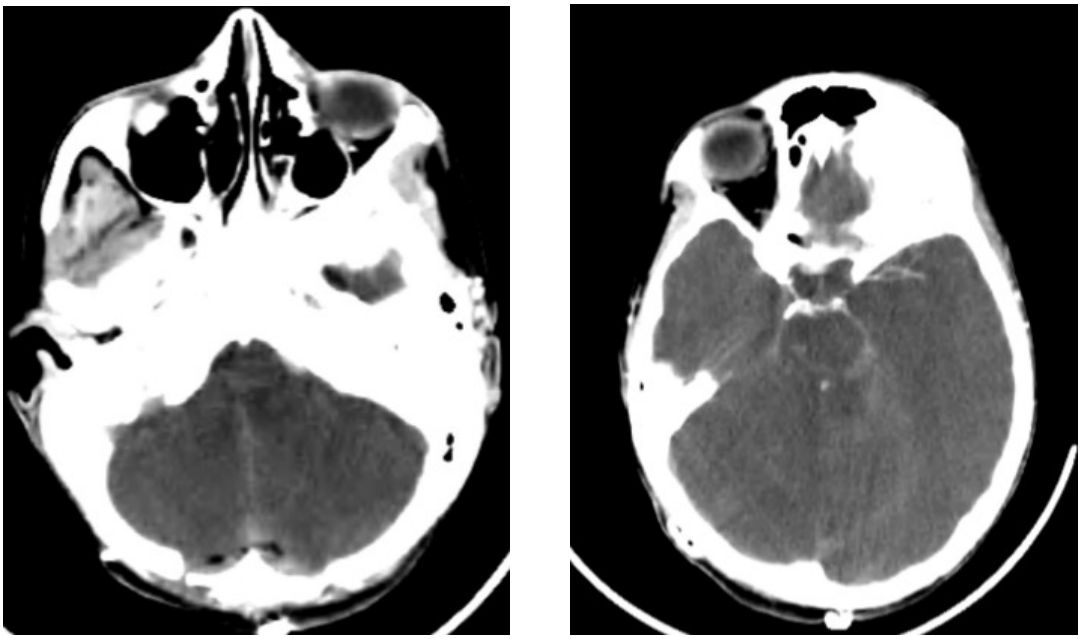


Figure 38 : cerebellar infarction following basilar artery injury per op during the resection of medulloblastoma in this patient.

COMPLICATIONS	Number
Post operative hematoma	3
Intracranial suppurations	10
Wound infection and meningitis	17
Cerebrospinal fluid leak	20
Basilar artery ischeamia	1
Hydrocephalus	11
Death	7

During our study ze noted 7 cases of patients who died within the first year following surgery. Causes were related to either

- Infections: either immediately following surgery or after adjuvant therapy with opportunistic infections
- neurovascular (basilar artery infarction)
- tumor recurrence with tumor size large enough to compress the brainstem

8. Adjuvant therapy.

8.1. Radiation therapy.

Among patients retrieved, we found that 13 patients did not receive adjuvant therapy either through chemotherapy and radiotherapy.

We initiated therapy in a space of 30 days. Radiotherapy normally initiates for patients with no metastasis

Twenty-one patients had adjuvant therapy. All these patients received chemotherapy and radiotherapy. Radiotherapy involves 54 grays of radiation with 36 grays on the nevrax and the remaining 18grays a boost on the posterior fossa.

For micro metastatic dissemination of medulloblastoma a craniospinal irradiation is delivered to the entire brain and spine and given concurrently with primary site radiation for the first 13 days of therapy, to a total dose of 23.4 grays.

This treatment ptotocol is generally issued for children

Radiation therapy considerations in adults requires craniospinal irradiation with a boost to the primary tumor site. Adults received 36 grays of craniospinal irradiation as opposed to the 23.4 grays utilized in children.

8.2. Chemotherapy.

Chemotherapeutic treatment was issued in case of residual gross and micrometastatic disease

Chemotherapy was given within the first thirty days and this treatment includes vincristine, cyclophosphamide, Lomustine and cisplastin.

Treatment Overview

Surgery			Chemoradiotherapy								Maintenance								
	~30 Days		Radiation Therapy							~30 Days									
		Week	1	2	3	4	5	6	7		11	17	23	27	33	39	43	49	55
		Chemotherapy		V	V	V	V	V	V		A	A	B	A	A	B	A	A	B

V= Vincristine 1.5mg/m² (1 dose)

A= Cisplatin 75mg/m²(1 dose), Lomustine 75mg/m²(1 dose), and Vincristine 1.5mg/m²(3doses)

B = Cyclophosphamide 1000mg/m²(2 doses) and Vincristine 1.5m/m²(2doses)

9. Post operative metastasis

We noted metastasis among 12 patients despite an adequate adjuvant therapy. Some other patients did not receive adjuvant therapy on time

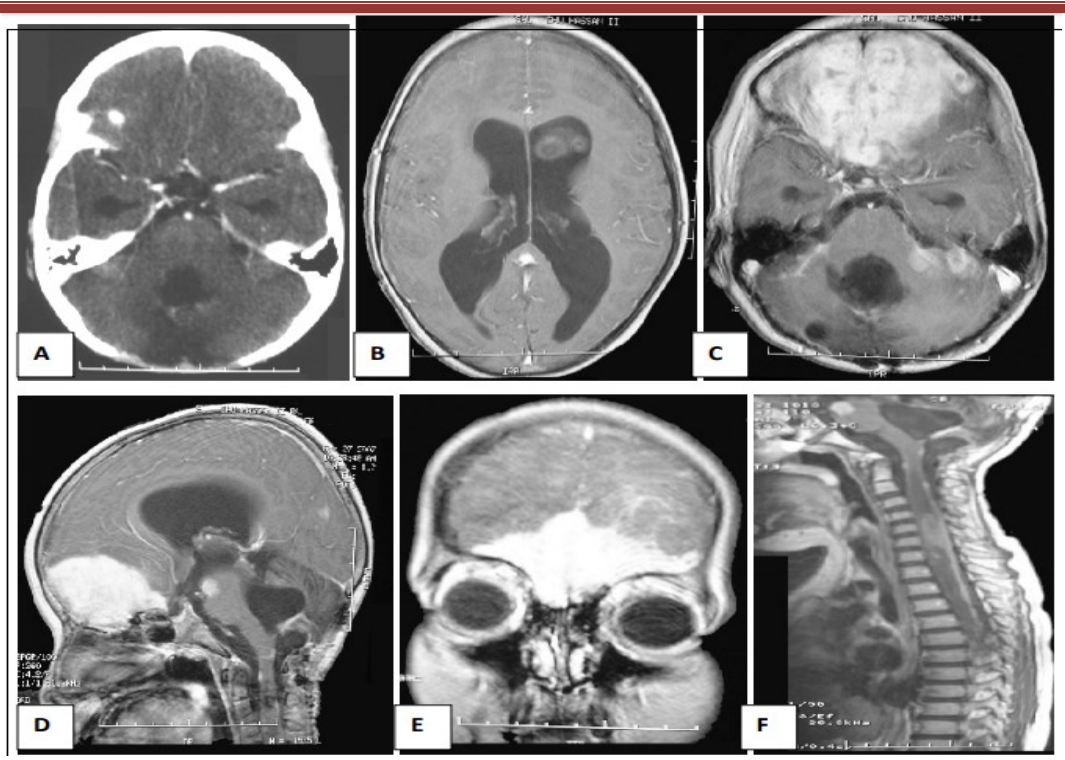


Figure 38 showing an injected contrast CT scan just some few days post operative.

Figure B, C, D, E, and F: MRI of the same patient 4 months post operative showing disseminated craniospinal metastasis.

10. Tumor recurrence.

We retrieved 4 cases of tumor recurrence during post operative images that were been conducted. The average time for tumor recurrence was 8 months. These patients were re-operated with poor prognosis.

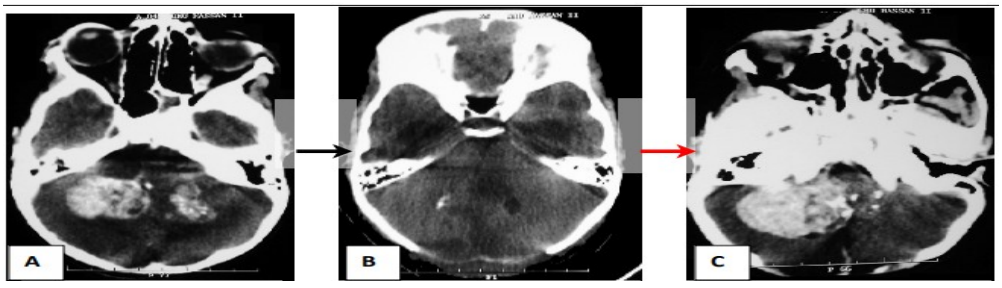


Figure 39: showing a subtotal resection of the tumor with a control that was done later showing tumor recurrence 11 months afterwards. This patient was a 4 year old patient who had received radiotherapyand and chemotherapy.Histopathology subtype could not be confirmed.

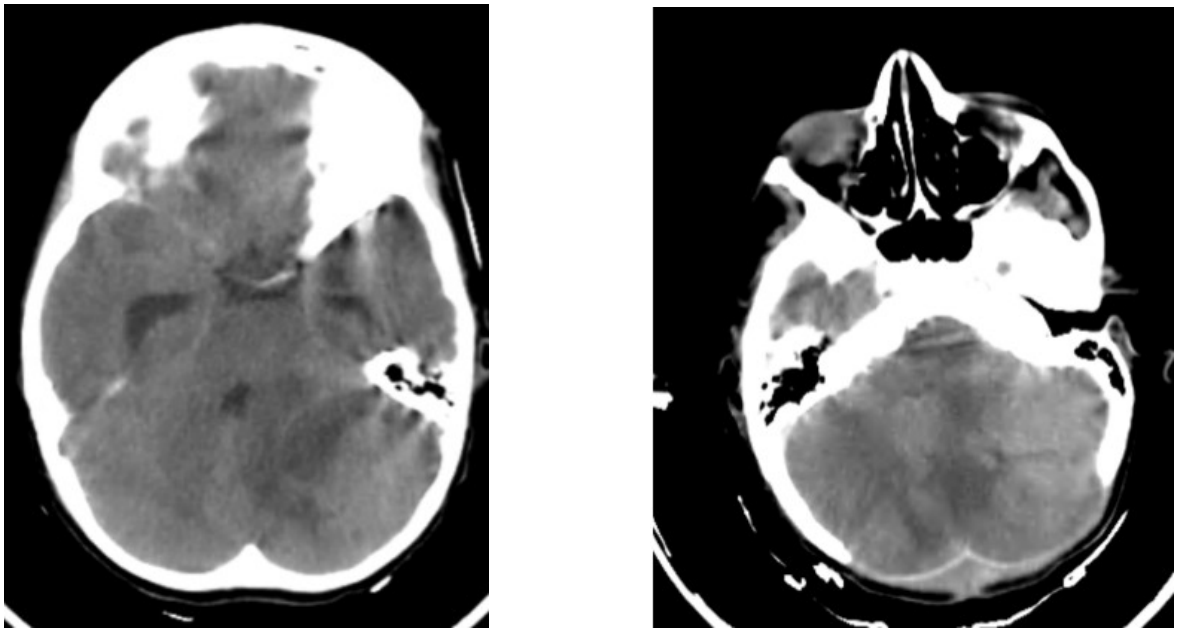


Figure 40: showing a resection of the tumor in 2 years old patient with recurrence of the tumor that appeared 2 months later after having received radiotherapy. Note that a residual tumor was left during the first surgery.

DISCUSSION

IV. DISCUSSION

Medulloblastomas are heterogeneous, highly aggressive tumors of the central nervous system and are the most frequent malignant brain tumors in children [91]. Most medulloblastomas are sporadic and arise in the posterior fossa due to deregulation of cerebellar development [92].

During our study at the neurosurgical department of fez, we retrieved 34 patients through a retrospective study from 2016 to 2019. This study presents

- clinical profile of patients
- surgical profile of patients
- histopathologic profiles of medullobalstoma
- management of patients adjuvant therapy
- complications
- tumor recurrence and metastasis

Our study retrieved within 3.5 years 34 patients despite the fact that we had many more potential patients to include in our study, they were excluded because of insufficient data necessary to build up our questionnaires.

a. Demographic data

Among the 34 patients retrieved, 12 were females with 24 men represented. The sexThe age group mostly represented was beteween 0-10 years old (44%). This finding is similar to others where a peak age is below 3 years old and becomes rare among the adult population [16, 17].

b. Histologic and genetic subgrouping.

Out of the 34 patients retrieved, approximately half of our study population had a clear histopathologic subtype specified in the histopathologic report.

We found that out of the 17, fourteen among them presented a desmoplastic medullobalstoma while just 3 presented classic medulloblastoma and none for the large cell or anaplastic subtype. This finding differs with that found in other studies where classic type is described in around 70% of cases of MB **[93].**

All of the classic forms were found in the 0 -10 age group but all above the age of 3 years old. This finding is also similar to other studies where classic types have two peak ages of onset, 10 years and 20 years, and rarely occur in children under 3 years **[94].** . In our study none of the classic types had less than 3 years but we had no case within the peak age age of 20. This can be also attributed to the non specification of the 17 other patients whose histology was not specified.

For the desmoplastic form, it represented 14 patients distributed between the 0-10 and 0-20 age groups. Seven among the 14 were less than 3 years old, 4 between 4-10 years old and 3 among the 11-20 age group. This finding partially meets previous studies a it, usually appears in two age groups: children below 3 years and adults **[95, 96].** None of our patients appeared among the adult population however we can attribute this also to the fact that all the population studied did not have specified histologic subtype. Our study however confirms also the strong representation of desmoplastic forms among infants less than 3years old.

Classic forms diagnosed in our study presented a strictly vermian midline localization of the tumor, this radiologic presentation coincides with other studies **[94].** The desmoplastic forms varied with 2 patients presenting a cerebello-vermian localization while the rest presented vermain localization. Other studies showed showed a correlation between cerebellar localization and desmoplastic **[94].**

Out of the 17 patients retrieved without histopathologic report 11 among them showed a vermian localization of the tumor while 6 others presented either cerebello-vermian or cerebellar localization. This finding is very present in many

other studies where the most common primary site for medulloblastoma localization is in the posterior fossa and in the vermis.

In our study no cases of large cell nor anaplastic forms were retrieved in our study. Our histopathologic reports did specify results for 50% of our patients. Large cell and anaplastic medulloblastoma (LC/A) subtype accounts for about 20% of diagnosed MBs **[93].** These tumors, known for their aggressive behavior, tend to metastasize via CSF and outside the CNS **[97].** However, LC/A MB might have a good prognosis if clinical risk factors, such as metastasis and young patient age, do not occur. Still, LC/A pathology is a high-risk factor (as well as metastases at presentation or high-frequency *Myc* amplification) **[98].** The table below illustrates the correlation between histologic profile, demography and molecular genetic profile.

Table 1 Characteristics of each subgroup of MB

	WNT	SHH	Group 3	Group 4
Prevalence	10%	30%	25%	35%
Age	Children, teens	Infants, adults	Infants, children	Infants, children, adults
Sex (M:F)	1:1	1:1	2:1	3:1
Histology	Classic	Nodular desmoplastic histology, classic, LCA	Classic, LCA	Classic, LCA
Metastasis	Low	Low	High	High
Recurrence	Rare	Local	Metastasis	Metastasis
Prognosis	Best	Intermediate	Poor	Intermediate
5-Year OS	95%	75%	50%	75%
Genetics	CTNNB1 DDX3X SMARCA4	MYCN, GLI2, PTCH1, SUFU, MLL2, SMO, TP53, BCOR1, LDB1, GABRG1	MYC, PVT1, OTX2, MLL2, SMARCA4, CHD7	OTX2, DDX31, CHD7, SNCAIP, MYCN, CDK6 GFI1/GFI1B, MLL2, KDM6A, MLL3, ZMYM3
Chromosome	chr 6 loss	chr 3q gain, chr 9q loss, 10q loss	chr 1q gain, chr 5q loss, 10q loss	Isochromosome 17q chr X loss, 17p loss
Cells of origin	Lower rhombic lip progenitors	Cerebellar granule neuron precursors	Neural stem cells?	Upper rhombic lip progenitors

LCA: large cell anaplastic.

Our study had no experience on the molecular genetic profiling of patients during our study. Genetic profiling could not be carried out because of the expensive cost which0020above the limits of patients. Some medulloblastomas are thought to arise from stem cells located in the subependymal matrix and the **external granular layer** (EGL) of the cerebellum. This layer is formed from

precursor cells that migrate from the rhombic lip to the surface of the developing cerebellum where they divide and differentiate. The EGL persists until the beginning of the second year of life. Different stem cells from the subependymal matrix around the fourth ventricle give rise to the cerebellar nuclei and Purkinje cells.

Clinical profile and imaging profiles.

Patients presented all symptoms and signs related to a mass in the posterior fossa. Cerebellar symptoms were retrieved in most cases inall cases and signs of raised intracranial pressure were noted during the study. These signs were all present in our study

All our patients benefited from at first head CT scan and an MRI. These patients always presented with hydrocephalus. This finding is similar to other studies where they retrieved about 93% of the study population [99]. In general patients with medulloblastoma present hydrocephalus. The higher proportion in our study is also attributed to an average tumor size of 3.5cm in diameter.

This is also attributed to a late diagnosis as most patients came from low income families; living in remote areas where the acces to imaging is often rare.

The imaging findings of cerebellar medulloblastoma in children is well established on CT images as a well defined, hyperdense and homogeneous midline mass with marked enhancement after IV contrast injection [100]. Nevertheless, atypical features, which include calcification, cystic or necrotic regions, ill-defined margins and lack of enhancement, should not be considered against the diagnosis of medulloblastoma in the first decade of life [101]. These findings are similar in our study.

Regarding the MRI features, Koci et al [102], had similar preoperative T1 weighted images showed hypointense tumors, isointense to gray matter in some oyher cases and a hyperintense mass in one case. This is finding on T1 images was

similar to our study. T2-weighted images revealed diversified images either; hyperintense tumor, slightly hyperintense, and isointense tumors which was similar to other studies.

Risk stras

Treatment options.

Out of the 34 patients retrieved, 28 had shunting either by ventriculoperitoneal shunt (19 cases) or ventriculocisternostomy (9 cases) before surgery. Indications for this surgery were raised intracranial pressure and this was always done in an emergent situation.

Usually time lapse before surgery was 54 days. This delay was usually due to some technical problems encountered in the surgical room but also owing to many other emergency cases that had to be taken in charge.

Surgery adopted to 34 patients was more of the transvermian approach than the telovelar approach. In our study, the transvermian approach was preferred in cases of vermian localization of medulloblastoma. However the telovelar approach was indicated in our study in cases of cerebello-vermian localization of the medullolastoma. The techniques also depended on the surgeon's choice. Of the 34 patients operated, 19 had a complete resection of the tumor with the remaining been subtotal or partial resections. Reasons for an incomplete resection where always due to infiltration of the tumor in the floor of the fourth ventricle or of the brainstem. This attitude is recommended by many other authors **[44]** to avoid the resection of tumors infiltration important neural structures of the posterior fossa.

For all patients retrieved post operative imaging were always a head CT scan. This finding is different with some other studies where MRI is the post operative imaging of choice **[67]**; MRI has been proven a better post operative control than the CT scan. Our patients did not benefit from MRI because its avaibility for post

operative controls as well as diagnostic tool could not be technically possible as just one MRI machine is available for the hospital.

We registered 21% (7 out of the 34) of death cases. This percentage is higher by two folds with respect to other studies [18]. The etiologies were similar to other studies. In our study the first etiology was related to infectious complications (post operative meningitis, intracranial suppurations) following usually CSF leakage. However we noted a rare case of cerebellar infarction due to basilar artery injury. Some other complications involve hydrocepahalus, cerebellar mutism.

Cerebellar mutism was always found in 2 patients who underwent the transvermian approach. This coincides with other findings as cerebellar mutism generally results from splitting the vermis.

All complications registered were present in other studies [10, 56, 88].

Adjuvant therapy was always proposed in patients. The medical oncology and radiotherapy departments propose a treatment regimen following based on the International Society of Paediatric Oncology (SIOP) which has a committee named Paediatric Oncology in Developing Countries (PODC). This protocol was applied for our patients and this considered classifying patients either into standard and high risk groups. This protocol was adapted for children.

In our study patients were considered standard and high risk either by

Standard risk medulloblastoma	High risk medulloblastoma
All of the following:	Any one of the following:
>3 years of age	<3 years of age
<1.5 cm^2 residual tumour after resection	Subtotal resection (>1.5 cm^2 residual)
CSF negative for tumour cells on L.P.	CSF positive for tumour cells
MRI spine negative for leptomeningeal spread	MRI shows leptomeningeal spread
Classic or desmoplatic subtypes on pathology	Large cell or anaplastic subtype
Complete staging possible	Incomplete staging

In our study out of the 34 patients retrieved 10 among the paediatric population were considered high risk;

- 3 post operative images showing a subtotal resection with a residual volume estimated to be more than 1.5cm2
- 5 patients were less than 3 years of age.
- There was a leptomeningeal on post op craniospinal MRI that was demanded by the paediatric oncology department.

This table below illustrates the radiotherapy protocol options that was to patients

- Patients with incomplete staging should receive full dose CSI (36 Gy + Boost).
- Patients unable to attend for adjuvant chemo should receive the full dose CSI protocol.
- CSI should commence within 40 days of surgery. Patients delayed longer than 49 days after surgery, should receive at least one cycle of chemotherapy (but no more than two) and be treated with full dose CSI.
- 3D planning of the boost gives superior cochlea sparing.
- RT should be completed within 50 days.
- Baseline height, weight and endocrine function (as described in the text) should be obtained prior to RT.
- Weekly FBC is required to monitor for myelosuppression during RT.

Indications for CSI in PODC medulloblastoma	Reduced dose CSI –23.4 Gy - Age >3 years - Total macroscopic resection (residual $<1.5\,cm^2$ on post-op imaging) - Spinal MRI clear - CSF clear	Full dose CSI –36 Gy - Spinal lesions on imaging - CSF positive - Incomplete staging o No spinal MRI o No CSF cytology o Unknown extent of resection - Unable to attend for chemo
Dose of large volume (4–5 × 1.8 Gy/week)	23.4 Gy in 13 fractions	36.0 Gy in 20 fractions
Dose of Boost Fractions	30.6–32.4 Gy in 17–18 fractions	18–19.8 Gy in 10–11 fractions

This findings were those adopted at the radiotherapy department for these patients. Our study initiated a treatment option 30 days after surgery and the treatment had a duration of 30 days. Adults received a full dose CSI of 36 grays with a boost dose.

Chemotherapy regimen also followed the PODC protocol for children and similar drugs for the treatment options.

Out of 34 retrieved, 25 received adjuvant therapy, 6 patients died on post op and 4patients did not show up for treatment.

Tumor recurrence was observed in 4 patients and this was noted among patients where the tumor resection was subtotal. Despite the administration of an adjuvant therapy, these patients reccured in an average of 11 months post operative. This finding is in accordance with other studies presented recommending maximal resection at most less than 1.5 cm2 to avoid recurrence.

Metastasis was also noted in our patients. This involved spinal, cerebral and leptomeningeal dissemination. This finding is similar in our study and found in many other studies **[74].**

CONCLUSIONS AND RECOMMENDATIONS

V. CONCLUSIONS AND RECOMMENDATIONS

At the of this study we can conclude the following in our study

a. Medulloblastoma is a common malignant tumor of the posterior fossa in our department.
b. Medulloblastoma is more present among children tha, adults.
c. Patients generally present with signs of raised intracranial pressure and usually always receive diversions either through ventriculoperitoneal shunts or ventriculocisternostomy.
d. In our department both the telovelar and tranvermian approaches are done with a greater proportion from tranvermaian approach despite a late time lapse from admission to tumor resection.
e. Complications like hydrocephalus, infections and CSF leak are most common complications in our department.
f. Histological reports partially attends to list the subtype.
g. No genetic molecular subgroupig is done so far in our hospital.
h. Adjuvant therapy is been done efficiently in our hospital.

At the end of this study we can propose the following recommendations

1. The medical file of patients should be appropriately filled and taken of so as to ease research studies
2. Preoperative images should be well documented that is tumor siwe and volume as it permits to stratify patients according to high or standard risk patients
3. The time lapse for surgery should be considerably shorten and time frame of 7 days at lost be adopted. This considerablt reduces the morbidity and mortality of patients

4. Post operative images should be MRI not CT scan because medulloblastomas are malignant and the detection of a residual tumor, its volume, changes the therapeutic approach of the adjuvant therapy.
5. Efforts should be done to specify histopathology and molecular genetic subgroups of medulloblastomas because the recent stratifications relies dominantly on molecular gnetic considerations.
6. The approach should be multidisciplinary between neurosurgeons, oncologists, radiotherapists, histopathologists, radiologists and paediatricians. This will permit a better management of patients and avoid the missing of some patients.

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VI. REFERENCES

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