Medulloblastomas (MBs) are the most common malignant brain tumors in children. Current therapeutic approaches combine surgery, radiotherapy, and chemotherapy. Although, there has been significant improvement in long-term survival rates, the tumor remains incurable in about a third of patients while cognitive deficits and other sequelae of therapy are common among long-term survivors. Hence a major challenge remains to differentiate high-from low-risk patients and to tailor therapy based on the degree of biological aggressiveness. A clinical risk-stratification system has been widely used in MBs based on age, extent of resection and the Chang staging system. However, recent reports indicate that these clinical variables are inadequate methods of defining disease risk. This has prompted search for new markers for MB stratification. Recent studies indicate that the classification of MBs according to profiles of histopathology and molecular abnormalities possibly help better risk-stratification of patients, thereby rationalizing approaches to therapy, increasing cure rate, reducing long-term side effects and developing novel therapeutic strategies. The most accurate outcome prediction till date has been obtained through microarray gene expression profiling. In this article, the current histopathological classification and the recent advances in molecular genetics of MBs are reviewed. Global efforts to translate this knowledge of disease biology into clinical practice especially as outcome predictors are highlighted.

Key words: Histopathology, medulloblastoma, molecular genetics, prognostic factors, risk-stratification.

Medulloblastoma (MB) is one of the five embryonal tumors of the central nervous system (CNS) included in the current WHO classification (WHO Grade IV).[1] It is a highly malignant tumor of the cerebellum occurring predominantly in children and accounting for 12-25% of all pediatric CNS tumors.[2-4] It is less frequent in adults, constituting only 0.5-1% of all intracranial neoplasms.[5-11]

A. Risk stratification by clinical factors

Since the mid-1990s, the risk classification for relapse and selection of treatment of MB patients has remained strictly clinical, with cases stratified into two-risk groups, viz. ‘average risk’ and ‘high risk,’ based on the following criteria: (i) age, (ii) extent of resection, and (iii) Chang metastasis staging [Table 1].[12,13]

According to this classification, average-risk patients are those older than 3 years of age with nonmetastatic disease and totally or near totally resected tumors (<1.5 cm of residual tumor on postoperative MR). Patients not fulfilling these criteria are regarded as high-risk. This clinical staging has been helpful as a broad

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<th>Stage</th>
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<td>T stage</td>
<td>Description</td>
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<tr>
<td>T1</td>
<td>Tumor less than 3 cm in diameter and limited to the midline position in the vermis, the roof of the fourth ventricle and less frequently cerebellar hemisphere</td>
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<td>T2</td>
<td>Tumor more than 3 cm in diameter, further invading one adjacent structure or partially filling the fourth ventricle</td>
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<td>T3</td>
<td>Divided into T3a and T3b</td>
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<td>T3a</td>
<td>Tumor invading two adjacent structures or completely filling the fourth ventricle with extension into the aqueduct of Sylvius, foramen of Magendie or foramen of Luschka, thus providing marked internal hydrocephalus</td>
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<td>T3b</td>
<td>Tumor arising from the floor of the fourth ventricle or brain stem and filling the fourth ventricle</td>
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<td>T4</td>
<td>Tumor further spreading through the aqueduct of Sylvius to involve the third ventricle or midbrain or tumor extending to the upper cervical cord</td>
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<td>M stage</td>
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<tr>
<td>M0</td>
<td>No evidence of gross subarachnoid or hematogenous metastasis</td>
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<tr>
<td>M1</td>
<td>Microscopic tumor cells found in cerebrospinal fluid</td>
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<td>M2</td>
<td>Gross nodule seedings demonstrable in the cerebellar, cerebral subarachnoid space or in the third or lateral ventricles</td>
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<td>M3</td>
<td>Gross nodule seedings in the spinal subarachnoid space</td>
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<td>M4</td>
<td>Extraneuraxial metastasis</td>
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guide for predicting prognosis. However a major drawback is that this does not differentiate high- from low-risk patients within the same clinical stage. It is a well-observed fact that patients with similar neoplasms and similar clinical stage, receiving identical therapies can have widely disparate clinical outcomes, owing to biological differences within the tumor.\[14] Further, two different trials, German trial HIT’91 and CCG 921\[13,15]\ have established that overall survival (OS) is not significantly different between children staged as M0 vs those staged as M1. Also, brain stem invasion (stage III b), previously regarded as an indicator of high-risk, is now believed not to affect prognosis.\[13]\[15]

Based on this clinical staging system, a multimodality therapeutic approach has been designed for MBs, with maximum surgical resection, neuraxis radiation and chemotherapy.\[16]\ This has led to a reduction in the mortality rate by twofold in the last 30 years, with OS rates ranging from 50 to 60% at 5 years and 40-50% at 10 years.\[17]\ However, in long-term survivors of MBs, this aggressive protocol is associated with severe side effects in the form of neuropsychological sequelae and neurocognitive decline.\[18-21]\

In short, the major criticism of the current clinical staging is that it does not identify the 20-30% of *average-risk* patient with resistant disease or the *average-risk* patients who might be over treated with the current protocol.\[18]\ Hence, an important goal is to improve the chances of survival for all children with MB, and to tailor specific therapies to individual lesions based on both their degree of clinical as well as biological risk, so that patients are not over- or under-treated, and side effects are minimized.

All this has prompted search for new biological markers - histological and molecular - for MB stratification. It is hoped that a greater understanding of MB biology will not only translate into refinements in risk classification, but also lead to risk-based tailoring of therapies to individuals. It will also help in improvements in the way existing therapies are used, which is crucial in minimizing their devastating long-term side effects.

### B. Risk stratification by histopathological factors

Recent studies have conclusively demonstrated that the following three histological factors have a distinct role in the determination of clinical outcome in MB viz. histopathological subtype, extent of nodularity and grade, as well as, extent of anaplasia (Table 2). The other factors implicated to have prognostic significance include desmoplasia, cell differentiation, proliferation, apoptosis, and ploidy. However, their definite role still remains controversial.

#### 1. Histopathological subtypes

Six distinct histological subtypes of MB have been included in the current WHO classification.\[4]\ Classic MBs are characterized by sheets of densely packed cells with hyperchromatic small round to oval nuclei, indiscernible cytoplasm, numerous mitoses, conspicuous apoptosis, and formation of occasional Homer Wright/neuroblastic rosettes.\[4,22,23]\ Desmoplastic MBs, on the other hand, show typical nodular architecture comprising of reticulin-free pale nodules and reticulin-rich internodular regions.\[4,22,23]\ Medulloblastomas with extensive nodularity and advanced neuronal differentiation (MBEN) are a distinct subtype, occurring in infants less than 3 years of age and demonstrating a striking grape-like nodularity on imaging.\[24]\ Histologically, they show a predominant nodular architecture with round uniform cells inside nodules arranged in a streaming pattern within a fine fibrillary neuropil-like matrix. Thus they differ from desmoplastic MBs in showing uniform neuroectopic differentiation with little or no internodular component.\[4,22,23]\ LC/A MBs comprise of large cells with pleomorphic nuclei, prominent nucleoli and more abundant cytoplasm than most MBs. High mitotic and apoptotic rate along with large areas of necrosis are also common.\[4,22,23,25]\ Melanotic MBs, are characterized by melanin production in

<table>
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<th>Table 2: Risk groups for medulloblastoma</th>
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<td><strong>Factors</strong></td>
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<td>Age</td>
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scattered cells,\(^{26,27}\) while medulloblastomas consist of cells displaying variable rhabdomyoblastic differentiation,\(^{28-33}\) both in a background of classic MB.

Of all the six variants the best prognostic outcome is noted with MBENs.\(^{24,25}\) This is intriguing because it generally affects young infants who according to the clinical stage belong to the high-risk category. The worst outcome is associated with LC/A MBs, which are extremely aggressive with high incidence of local recurrence, CSF spread, systemic metastasis and death within 1-2 years of diagnosis.\(^{25,33}\)

Difference in prognosis between the classic and desmoplastic variants remains controversial. Desmoplastic MBs have been variably correlated with better outcome\(^{24-35}\) by some, while others found it to be either associated with worse prognosis,\(^{36}\) or without any correlation with survival time.\(^{9,38,39}\)

Melanotic MBs and medulloblastomas have poor outcome, with survival ranging from 2 months to 2.5 years, in the former, and generally less than 1 year, in the latter subtype.\(^{26,29}\)

### 2. Extent of nodularity

Eberhart et al.\(^{38}\) demonstrated nodularity in 29% of 330 similarly treated cases of pediatric MB from the Pediatric Oncology Group (POG, USA). However, nodule formation in MBs can be variable – from diffuse to very focal. Hence, they graded the extent of nodularity into five categories - extensive (96-100%), widespread (51-95%), moderate (11-50%), slight (1-10%), and none (0%), and observed that only tumors with extensive nodules were associated with better survival. All other grades of nodularity showed no correlation with outcome.\(^{38}\)

### 3. Anaplasia

The concept of anaplasia in MBs is relatively new\(^{14}\) and analogous to anaplasia in Wilms’ tumor, which has well defined clinical implications.\(^{40}\) Anaplastic MBs have currently been proposed as the variant with most aggressive biological behavior.

Anaplastic MBs are characterized by markedly atypical cells having angular pleomorphic nuclei with coarse chromatin, wrapping around each other, with frequent moulding.\(^{14,38,41,42}\) Earlier studies suggested that anaplasia was only confined to the large cell variant of MB. However, recent studies have shown that they can also arise by malignant progression of classic and desmoplastic MBs, as well as medulloblastomas.\(^{14,42,43}\) These cells are thought to represent focally aggressive clones capable of undergoing malignant progression, based on the observation that they often co-exist focally within MBs, or manifest only after recurrence or metastasis.\(^{14,41-45}\)

Brown et al.\(^{41}\) in a review of 474 MBs from POG patients, reported that the long-term survival of LC-MB with anaplasia was 10% compared to more than 50% in LC-MB without anaplasia. Eberhart et al.\(^{38}\) on reevaluating 330 of the POG patients reported by Brown et al.\(^{40}\) observed that while tumors with diffuse anaplasia were most aggressive, even focal anaplasia was significantly associated with poor outcome. Further patients with tumors having moderate to severe anaplasia (anaplastic group) had significantly shorter event-free survival (EFS) and OS as compared to those with slight to no anaplasia (nonanaplastic group). The 5-year survival probability was 42% in patients with anaplastic variant in contrast to 68% for patients with nonanaplastic disease. In fact, on log-rank analysis, grade of anaplasia allowed better stratiﬁcation of patients with respect to outcome than the current clinical stage, indicating that histological grading is not a surrogate for clinical staging, but rather an independent predictor of survival. Similar results of association of anaplasia with poor outcome have also been shown by MacManany et al.\(^{41}\)

### 4. Desmoplasia

Conflicting reports on relationship of desmoplasia to outcome are chiefly attributable to different definitions of desmoplasia.\(^{42}\) In addition to conventional desmoplastic MBs, rarely MBs show an intense pericellular desmoplasia without any obvious nodule formation. Further invasion of leptomeninges by classic MB also produces intense desmoplasia.\(^{42}\)

In a retrospective review of 330 POG patients, Eberhart et al.\(^{38}\) noted desmoplasia in 22% of cases. However there was no significant association of desmoplasia with clinical outcome (either EFS or OS).

### 5. Cell differentiation

Another histopathological prognostic parameter in MBs, which has received considerable attention but little agreement, is differentiation along glial or neuronal cell lines.\(^{40}\) Positivity for GFAP have been variably correlated with better prognosis,\(^{47,48}\) by some, while others found it to be either associated with poor prognosis,\(^{49,50}\) or without any correlation with survival time.\(^{51,52}\)

### 6. Proliferation labeling index (LI)

Cell proliferation is another prognostic parameter whose significance is not clear. Ito et al.\(^{51}\) showed that tumors with Bromodeoxyuridine (BudR) LI greater than 20% had a trend to worse prognosis. In contrast, Giordana et al.\(^{57}\) and Schiffer et al.\(^{53}\) showed no correlation in both adult and pediatric MBs. Studies of Sarkar et al.\(^{56}\) suggested that MBs in children have higher MB-I proliferative indices and lower apoptotic indices than those in adults.

### 7. Apoptotic index (AI)

Since it is the balance between cell proliferation and cell death that determines the rate of tumor growth, the impact of apoptosis on outcome has also been considered. Apoptosis has been suggested as a favorable prognostic feature by some\(^{55}\) and as a negative feature by others.\(^{56,57}\) Korshunov et al.\(^{57}\) calculated AI of >1.5% to be associated with shorter survival, while Eggert et al.\(^{58}\) found that expression of Apo3 was significantly associated with prolonged survival of MB patients. Hasham et al.\(^{55}\) demonstrated that patients with a high AI had substantially improved outcome compared to all other patients, independently from the assignment to a high- or low-risk group at the time of diagnosis.
8. Ploidy

A more favorable prognosis has been associated with aneuploidy in MBs. Ramanachandran et al\(^{59}\) found that patients with aneuploid tumors responded well to treatment regimens as compared to those with diploid tumors. Also, patients with progressive disease had a high S-phase fraction in the tumor cell population as compared with patients with favorable response to treatment.

C. Risk stratification by molecular and cytogenetic factors

It is widely accepted that identification of genetic and molecular alterations allows a clinically relevant subgrouping of MBs with particular profiles of biological behavior and outcome (Table 2).\(^{60-66}\) The molecular genetic alterations in MBs have been worked out extensively and can be divided into three heads:

1. Nonrandom chromosomal abnormalities,
2. Gene profiling,
3. Abnormalities in signal transduction pathways.

1. Nonrandom chromosomal abnormalities

(i) Loss of 17p/iso chromosome 17q

The most frequent genetic alteration present in 30–50% of MB cases is partial or complete deletion of the short arm of chromosome 17 (17p),\(^{67-71}\) which may occur in isolation, but more frequently as a component of an isochromosome of 17q [i(17q)].\(^{68,72-74}\) A recent study suggested that 17p loss/iso chromosome 17q is more frequent in LCA/MBs than in classic MBs.\(^{14}\)

Several authors have observed that 17p deletion and/or i(17q) are prognostically unfavorable being associated with poor response to therapy, metastatic disease and shortened survival.\(^{75,76}\) However, other studies have refuted this suggestion.\(^{72,77}\) Scheurlen et al\(^{76}\) reported that MBs with concomitant 17p alterations and c-myc alterations have worse prognosis, indicating possible interaction between these two genetic alterations in promoting aggressive behavior.

Mutations of the tumor suppressor gene, p53, located at 17p13.1 region are infrequent in MBs.\(^{78,79}\) However, an association of intense p53 immunostaining with significant reduced disease-free survival in MB patients has been shown by Woodburn et al\(^{80}\) Similarly, hypermethylation of the HIC-1 gene, on 17p13.3 region has been demonstrated to be a predictor of poor outcome in MB.\(^{81}\)

(ii) Myc gene (c-myc and N-myc) amplification

Amplification of c-myc and/or N-myc occurs in 5–10% of MBs, being most commonly associated with the LCA variant.\(^{45,82-87}\) Eberhart et al\(^{45}\) found amplification of c-myc in 4 (12%) and N-myc in 5 (15%) of 33 MBs, all with anaplastic foci. A very high rate of c-myc amplification of 17% was reported by Scheurlen et al\(^{76}\) among a population of clinically high-risk MBs.

There is clear evidence that patients whose tumors show c-myc gene amplification have worse clinical outcome, being resistant to therapy and having an aggressive course with short survival and fatal outcome. Aldosari et al\(^{83}\) found 4 of 77 MBs with c-myc amplification (5.2%) all of whom died within 7 months of diagnosis. One case having amplification for both c-myc and N-myc and four cases with only N-myc amplification were also associated with short survival time. In the series of Badali et al\(^{84}\) no long-term survivors were observed among cases with c-myc amplification. Similarly Scheurlen et al\(^{76}\) showed that all tumors with c-myc amplification were resistant to therapy and had fatal outcome.

A similar negative correlation of outcome with c-myc mRNA levels was shown by Herms et al\(^{85}\) and Grotzer et al\(^{86}\). Around 42% of MBs showed c-myc mRNA expression, and this parameter was found to be an independent prognostic criteria and more predictive than standard clinical factors.\(^{87}\)

High rate of immunopositivity for both c-myc protein (90%)\(^{89}\) and N-myc protein (84%)\(^{90}\) have also been reported in MBs. A tendency of N-myc immunopositive MBs to be associated with poor outcome was shown by Morinchi et al.\(^{90}\) Hence there is a need of identifying MBs with nyc gene amplification or nyc mRNA over expression, since a large body of evidence now indicates its association with aggressive clinical behavior.

(iii) Other chromosomal abnormalities

In 20–40% of MB cases, loss of chromosomes 1q and 10q has been demonstrated.\(^{91,92}\) Isolated examples of deletions of 3q, 6q, 9q, 10q, 11p, 11q, and 16q as well as gains of distal regions of 4p, 5p, 5q, 7q, 8q, and 9p have also been detected in MBs.\(^{81,93,94}\) However, till date no prognostic correlation has been attached to any of these chromosomal abnormalities, with the exception of 9q loss (locus of PTCH Gene). Lusher et al\(^{81}\) has reported inactivation of the Rb-like I4 gene on chromosome 3p21 in 79% of MBs (both in adult and pediatric MBs and in all histological variants).

Recently, Tong et al\(^{81}\) performed the first genomic survey of multiple oncogenes amplifications involved in the development of MBs. For the first time they identified gene amplifications involving PGY1 at 7q21.1, MDM2 at 12q14.3-4q15, and ERB2 at 17q21.2, by performing comparative genomic hybridization (CGH) and array-based CGH, in a series of 14 cases. Overall the highest frequency of oncogene gains was observed in D17S1670 (61.5%), PIK3CA (46.2%), PGY1 (38.5%), MET (38.5%), and CSE1L (38.5%). Gene amplification in MBs was further confirmed by using fluorescence in-situ hybridization (FISH) analysis in 34 additional archival MB cases. In future, gains in these genes may possibly qualify as candidates for molecular markers and therapeutic targets of MBs.

2. Gene profiling

Pomeroy et al\(^{87}\) studied gene expression profile of MB cases using oligonucleotide microarrays. The genes most closely correlated with MBs were ZIC and NSCL1, which encode transcription factors specific to cerebellar granule cells. They also identified a number of genes, which correlated with favorable outcome, including many genes characteristic of cerebellar...
differentiation (vesicle coat protein β-NAP, NSCL1, TrkC, sodium channels), and genes encoding extracellular matrix proteins (procollagen-lysine-2-oxoglutarate 5-dioxygenase, lysyl hydroxylase, collagen type V α1-I, elastin). In contrast, genes related to cerebellar differentiation were underexpressed in poor prognosis tumors, which were dominated by the expression of genes related to cell proliferation and metabolism [MYBL2, enolase I, LDH, HMG1 (Y), cytochrome C oxidase] and multidrug resistance (sorcin gene).

Their study further demonstrated that outcome predictions based on gene expression (with a model made up of eight genes) was statistically significant: patients with a certain pattern, expected to have a good prognosis, had a 5-year OS of 80% compared with 17% for those not having that pattern, for whom a poor outcome was predicted.

In another study of gene expression profiles, MacDonald et al[62] described that the platelet derived growth factor receptor alpha (PDGFR-α) and the Ras/mitogen-activated protein (MAP) kinase pathway genes were significantly upregulated in metastatic (M+) tumors but not in nonmetastatic (M0) MBs. This finding suggests that the PDGFR-α and Ras/MAP kinase signal transduction pathway may be rational therapeutic targets for M+ disease.

3. Abnormalities in signal transduction pathways

(i) Neurotrophin signaling pathway – TrkC expression and outcome

This pathway plays a major role in cerebellar development. It comprises of the neurotrophin family, which includes a set of ligands viz. nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), neurotrophin factors 3, 4, and 5 (NT3 and NT4/5). These are essentially trophic factors for the growth differentiation, survival and apoptosis of neurons. The other major constituent of this pathway are three members of the tyrosine kinase receptor family viz. TrkA, B, C. These Trk proteins function as classical growth factor receptors, each binding to one of the four neurotrophins resulting in their activation and upregulation of second messenger signaling pathway systems.[62,107,108]

TrkC expression has been reported in 48–85% of MBs in different series.[102,103] This high TrkC expression has been found to be the single most powerful independent predictor of favorable outcome in MBs, independent of other clinico-pathological variants. It was Segal et al[104] who first reported 5-year survival rates as high as 89%, in patients having tumors with high TrkC expression, as compared to 46% for those with low TrkC expression levels. Subsequently Kim et al[105] in a study of 42 cases of MB found that the median survival in high expressers of TrkC was 92 months, in contrast to only 39 months for the low expressers. In a larger study of 81 MBs and 6 PNETs, Grotzer et al[106] reported a 4.8-fold greater risk of death in children with tumors having low TrkC mRNA expression. They identified TrkC mRNA expression as a powerful independent prognostic factor for predicting progression-free and OS. In another study,[68] they showed 100% progression-free survival in a group of PNET/MB patients having combined low c-myc and high TrkC mRNA expression in their tumors after a median follow up time of 55 months. Contradictory results have been reported by Gajjar et al[107] who found no correlation of TrkC expression with clinical outcome.

(ii) ErB receptor signaling pathway – ErbB2 expression and outcome

The class-I receptor tyrosine kinases (RTK1), also termed ErbB/HER receptors constitute a signal transduction pathway that is important in both cerebellar development and MB tumorigenesis.[107,108] Of the four members of this family viz. ErbB1, B2, B3, and B4, Erb B2 receptor appears to play a central role in MB tumorigenesis, along with neurogenin-1b (NRG-1b). ErbB2 expression has been reported in >80% of MBs, with co-expression of ErbB4 in 54% and expression of NRG-1b in 87.5% of tumors.[102,107,109–111] However, Gajjar et al[112] found ErbB2 expression in only 40% of tumors, most frequently in the LCA variant.

Association between reduced patient survival and increased ErbB2 expression has been demonstrated by several workers.[18,62,109–112] Gilbertson et al[110] first reported a 48% 10-year survival rate in cases with less than 50% ErbB2-positive tumor cells, while the corresponding figures for cases ≥50% positive cells was 10%. This prognostic significance was maintained in a further extension of the study to 70 cases, with 25-year survival rates for cases with <50% and ≥50 ErbB2 expression being 46 and 17%, respectively.[111] In the same study, they[111] also showed that co-expression of ErbB2 and ErbB4 significantly correlated with reduced OS, being independent of other clinical variables like age and tumor stage. Further, co-expression of all three components viz. ErbB2, ErbB4, and NRG-1b was significantly associated with presence of CNS metastasis at diagnosis.[107]

It has been shown that combined analysis of molecular and clinical factors gives better risk stratification than clinical factors alone. Thus in an analysis of 41 MBs, Gilbertson et al[107] found that sub-total tumor resection, metastatic disease at diagnosis, high expression of ErbB2 and isolated 17p loss, all negatively correlated with survival. Similarly Gajjar et al[114] in a study of clinical average-risk childhood MBs reported 100% 5-year survival in ErbB2-negative disease cases, as compared to only 54% in ErbB2-positive tumors.

(iii) Hedgehog – (SHH/PTCH) signaling pathway

Sonic hedgehog (SHH), the principal member of the hedgehog pathway, is a family of ligands, which are involved in cerebellar development by promoting replication of granule cells.[113] PTCH (patched) is a tumor suppressor gene located on 9q22.3, which encodes a trans-membrane PTCH protein product. This is activated by SHH and functions as part of a signaling pathway controlling normal CNS development.[114–116] The SHH/PTCH pathway has been implicated in the development of both sporadic
and heritable forms of MB. Mutations in several components of the SHH pathway occur in about 25% of sporadic MB cases, commonly being mutation of the PTCH gene, reported in 8–12% of tumors.[117–119] In patients with Gorlin’s syndrome or NBCCS who have germline mutations of the PTCH gene the lifetime risk of developing MB is about 4%.[114,116,128] It has been observed that MBs that carry mutations in the SHH/PTCH pathway preferentially but not exclusively show nodular desmoplastic morphology.[121,122] However, till date no association has been found of alterations in this signaling pathway with prognosis in MBs.

(i) Wingless (WNT/WG) pathway

The WNT pathway co-ordinates a diverse array of developmental processes including the proliferation and fate of neural progenitor cells.[122,123] The components of this pathway include β-catenin, the key transcriptional activator which in turn associates in the cytoplasm with a complex, which includes adenomatous polyposis coli (APC) gene, glycogen synthase kinase-3 (GSK3β) and AXIN-1.[122,123] Mutations in proteins of the WNT pathway, especially of β-catenin and APC gene occur in about 15% of sporadic MBs.[124–128] Mutations of APC gene are also the cause of Tuber’s syndrome, a tumor predisposition syndrome characterized by development of bowel tumours and MB.[129]

No correlation again has been found with this pathway and prognosis. However an increasing number of anti-cancer drugs are being designed to target this pathway. Cycloapamine, is one example of a plant-derived teratogen, that specifically inhibits the SHH pathway in MB cells, causing anti-tumor activity.[130]

Conclusion

There has been marked improvement in the 5-year survival rates in MBs from 2–30% in the 1970s to 50–70% currently. A major challenge, however, remains to differentiate high- and low-risk patients, and to individualize patient therapies, so as to prevent long-term side effects. In this regard, clinical staging alone has been shown in various studies to have its limitations. Two histological parameters currently assuming prognostic importance in MBs are the histopathological variant and grading of anaplasia. It is becoming apparent that homogenous lumping of all MBs as grade IV, highly aggressive neoplasms may be unjustified. The new concept therefore is to categorize MBs into favorable versus unfavorable histological groups, which is comparable to the classification used for peripheral neuroblastomas and Wilms' tumors. Molecular prognostic markers also hold promise, though global, multi-institutional studies with larger number of patients are required to prospectively validate their role as well as the methodologies used for the assessment of their expression levels.

The detailed mechanisms of how the different signaling pathways mediate an oncogenic effect need to be identified if we are to exploit these pathways fully for patient prognostication and management. Further, several questions need to be answered -which pathways initiate MB formation and which are involved in disease progression; how specific pathways affect MB histopathology and behavior; and whether any signal pathways mediate resistance to conventional treatments. It is possible that in such a complex interaction of several factors, a final scenario will emerge where in a combination of clinical, histopathological and molecular factors will provide a more reliable means of disease stratification in patients of MB, rather than any single parameter alone. The role of the Pathologist will then assume great importance in guiding clinicians regarding biological risk assessment and tailoring therapeutic strategies.

References


Sarkar et al: Risk stratification in medulloblastomas

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23