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B-Catenin Expression in Medulloblastoma: Prognosis and Favorable Outcome

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Abstract In our era of technology and progress in medical molecular biological science, it's now obligatory to think extraordinary to deal with the brain tumors, reaching the best prognosis for a better outcome. We focused on proving the strong relation between the subtypes of medulloblastoma and the magnificent rule of B-catan in nucleo-positivity in a Wnt/ wg pathway, associated with mutations like APC, CTNNB1 as a good diagnosis and prognosis of Medulloblastoma, It's mandatory applying these good prognostic factors in the prospective plan of treatment, using these factors like B-catenin nucleo-positivity in Wnt pathway subtype of medulloblastoma to reduce the dose of adjuvant therapy as radiotherapy and chemotherapy to reach a better result after management and to minimize the side effects of adjuvant therapy either chemotherapy or radiotherapy. In this manuscript we consider the past studies done from 2005 till 2012; talking about nucleo-positivity of B-catenin protein in medulloblastoma and the effect of it on prognosis, although the number of cases in these studies was not quite enough, but we can consider at least there is an evidence of association between positive B-catanin activity,Wnt/ wg pathway and good prognosis also for more specific approaches of treatment.

Keywords Medulloblastoma, B-catenin, WNT Pathway, Improved Outcome, Prognostic Factor, Radiotherapy, Craniospinal Irradiation CSI

1. Introduction

1.1. Purpose

In this manuscript, it is aimed to see what is the rule of β-catenin expression in the prognosis of Medulloblastoma, does it makes a difference to have a nucleo-positive or nucleo-negative subtypes of B-catenin in medulloblastoma, and can we apply this in the management of the medulloblastoma, to see what science has revealed on this subject seeking for further research and work.

1.2. Background

Medulloblastoma is one of the primary malignant brain tumors which is the commonest in childhood age, the new researches have revealed that there are many subgroups of it with different molecular, pathologic, and clinical presentations; all these can lead to modulate the approach on how we can modify the protocols of management of medulloblastoma to reach the best outcome, survival rate, and to get rid of the potential side effects of adjuvant therapy[3,4,5,6,9].

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1.3. Overview

Medulloblastoma is the most common malignant brain tumor in pediatrics, about 15% to 20% of all pediatric primary brain tumors[9], many studies with huge funds were done the past decade trying to find a solution for improving the outcome of this tumor group, studies were able to identify distinct subgroups within the medulloblastoma tumors big group regarding the molecular, histological, or even clinical levels. Studies have proven that there are 3 main categories WNT, SHH, and Non SHH/WNT subcategories[9], which may contain differences in between, there are many categories with special genetic expression, nuclear immuno-reactivity, or histological picture, even the age presentation and clinical presentation are even specific for each one of them.

β-catenin which is a protein encoded by CTNNB1 gene, is a subunit of cadherin protein complex, it is responsible for adhering junctions which control cell growth & proliferation, also it helps to anchor actin cytoskeleton, also contact inhibition which is considered one of tumor suppressor components[10].

It is a part from the Wnt signaling pathway, in normal cells with the presence of Wnt units, it will attach to frizzled Fz receptors to activate Dishevelled (DSH) units which in turn deactivate GSK3, and TrCP phosphorylation of β-catenin leading to release β-catenin leading to attach to

DNA through certain proteins stimulating polymerization, RNA and protein formation leading to stimulate cell development and proliferation. In the absence of Wnt signaling pathway, GSK3 with TrCP will phosphorylate β-catenin to go ubiquitination and degradation by proteasome to control cell proliferation and division leading ultimately to apoptosis[10].

In medulloblastoma, B-catenin mutation and Wnt pathway activation was suggested to be associated with favorable outcome[3,4].

The purpose of this literature review is to investigate the impact of nucleo-positive β-catenin/wnt pathway on medulloblastoma tumors as a prognostic factor in the clinical presentation of the disease to prove if it is associated with favorable outcome.

2. Methods

2.1. Search Strategy and Selection Criteria

We searched PubMed in 13 august 2012 for all studies related to our subject of interest using these keywords: β-catenin medulloblastoma, β-catenin AND improved outcome and, medulloblastoma AND improved outcome.

Got 71 results for β-catenin medulloblastoma, 20 results for β-catenin AND improved outcome and 79 results for medulloblastoma AND improved outcome. Excluded 153 abstracts where 15 abstracts are not associated to brain tumors at all, 24 abstracts are not related specifically to medulloblastoma, 58 abstracts didn't include β-catenin expression or, are concerned with chemotherapy for medulloblastoma, and 56 abstracts are not concerned about the role of β-catenin in medulloblastoma outcome and give a general idea about different molecular subgroups of medulloblastoma.

The remaining articles were reviewed, concerned about inclusion criteria for participants, study design and effect of immunohistochemistry techniques or any extra factor in the outcome. Also we include data only that are talking about β-catenin nucleo-positive medulloblastoma in children with the age range 3-16 years old, and exclude it in early childhood as this subtype of medulloblastoma is very rare under 3 years old, also in adults older than 16 years old due to that this subtype is less common in this age range with a different approach and better outcome, with exclusion to any paper before 2005.

3. Results

We read those papers, understood them, then reach the summary, and then we wrote each paper in a 1-2 paragraphs, wrote them alphabetically according to the last name of the first author.

In Clifford S., et al, (2006)[1], it was a report about two manuscripts one of them will be discussed later in this review Ellison D., et al, (2005)[5], but the second one was not included in this review because it was prior to 2005, Ellison D., et al, (2003)[2]. So we will only take what was discussed in this paper about the second one. A cohort study of 19 1ry medulloblastomas was assessed for evidence of Wnt/wingless pathway activation, alongside a Genome-wide association study"GWAS" CNAs by ar-CGH. Only 3/19 showed CTNNB1 mutations, 2 of them were associated with strong combined cytoplasmic and nuclear immunoreactivity for β-catenin. the 3 cases harboured a complete chromosome 6 loss, Chromosome 17 defects (the most common genomic defects observed in medulloblastoma patients) were never associated with Wnt/Wg pathway tumors, also some chromosomal defects which not common in medulloblastoma (gain of Ch.7, regional loss of Ch.8, 10, and 11) tended not to be in Wnt/Wg pathway tumor, but due to the limited study cases' number, these results did not reach statistical significance. Clifford S, et al in this report divided the 19 cases into 3 clusters A, B, and C but it did not add anything to the results and was not necessarily due to the limited number of cases. Clifford S., et al, (2006)[1].

A clinical cohort trial composed of 235 medulloblastoma patients from 0.4-52 year to show expression of 4 immunohistochemical markers in medulloblastoma patients, this study used FFPE tissues from 235 total medulloblastoma patients only 183 from them were children (aged 3-16 yrs) treated on SIOP/UKCCSG CNS9102 PNET3, only 32 of them were β-catenin nucleo-positive representing WNT pathway tumors, also Hematoxylin Eosin, Reticulin preparations, Antibodies to β-catenin were used with positive control tissues. Antibodies to β-catenin were effective on FFPE tissues for identifying WNT tumors, classic Pathologic medulloblastoma dominated the study about 72% of all tumors (235), β-catenin medulloblastomas differed from being cytoplasmic and/or nuclear immuno-reactive and the most important one was being nucleo immunoreactive medulloblastoma either associated with cytoplasmic or not, all WNT pathway tumors were classic (30) except 2 were Large cell/Anaplastic LC/A type, associated with Monosomy 6 in 25 WNT pathway tumors, most of the patients were represented in the range of 6-12 years, with Male : Female ratio 1.1:1, while OS and PFS shown the best outcome in WNT Pathway tumors (p= 0.02), other mutations in CTNNB1 gene, APC, and AXIN 2 have been recorded to be present in β-catenin nucleo-positive medulloblastoma either together or alone. This study has shown a good detailed method and clarified analysis but with a few numbers of cases as we only have only 14% of total 235 patients as WNT pathway tumors. Ellison D., et al, (2011)[3].

A cohort study (n=207) in patients aged from 3 - 16 years from the SIOP/UKCCSG CNS9102 (PNET3) trial having medulloblastoma to develop disease-risk stratification groups in order to individualize the treatment and reduce adjuvant therapy in subgroups with favorable outcome. Consequently, minimizing its long-term side effects of adjuvant therapy and vice versa. This study made three distinct stratification groups: high risk group associated with large-cell and anaplastic variants, a low risk group associated

with activation of Wnt pathway and having positive nuclear immunoreactivity for B-catenin and may be also associated with CTNNB1 mutation, and monosomy 6, and standard risk group without any of the previous features. Patients were randomly assigned to Craniospinal radiotherapy in addition to posterior fossa boost 35 Gy and 20 Gy respectively. Some were preceded by chemotherapy.

Formalin fixed paraffin embedded FFPE tissues were subjected to immunohistochemistry, also in-situ hybridization FISH, DNA extraction and analysis for CTNNB1 mutations were used. Wnt pathway activation was characteristic in Cells with strong nuclear B-catenin reactivity which was either widespread staining in the nucleus and cytoplasm of all cells, or focal with weak B-catenin immunoreactivity found in cell clusters. They used the three methods to define the variables that will be used in the classification of patients into subgroups, each group having specific therapy. Of 207 patients, 133 were alive without disease, 74 deaths (68 from the diseases), M stage was significantly associated with progression-free survival (PFS) and overall survival (OS) but age, sex and type of adjuvant therapy was not.

B-catenin nuclear immunoreactivity were shown in 33 (16%) of 206 tumors of 207 patients, 21 had strong widespread staining and 12 had patchy strong or weak staining with no significant outcome differences between them. CTNNB1 mutation was demonstrated in 21 of 31 B-catenin nucleopostitive tumors that underwent mutation analysis and wasn't found in any B-catenin nucleo-negative tumors (n=164). Monosomy 6 was demonstrated in 24(80%) of 30 of 33 B-catenin nucleo-positive tumors and was found in a few B-catenin nucleo-negative tumors with no significant effect on outcome. Of the 33 nucleo-positive, 5 patients (15%) died; 2 of them didn't die from the disease, one died from high-grade glioma and the other from the adverse effects of therapy. The other three, one was presented with m3 tumor and the other had MYC amplification. According to the previous results, cases with nucleo-positive B-catenin reactivity, CTNNB1 mutation and monosomy 6 are associated with good prognosis where the presence of any of the last two factors alone or in combination with B-catenin immunoreactivity doesn't have a better prognosis than B-catenin immunoreactivity alone. Ellison D., et al, (2011)[4].

A cohort study on 109 medulloblastoma patients from SIOP/UKCCSG PNET 3 were done to identify if the pathobiological status of medulloblastoma makes a difference in therapeutic methods application and decreases adverse effects of adjuvant treatment, and if the presence of nucleo-positive β-catenin and the possibility of its association with APC and CTNNB1 mutations makes any difference in the prognosis of medulloblastoma, using FFPE tissues for the samples of the tumors, histopathologically; classic tumors(n=89 from 109) and LC/A variants (n=20 from 109), with male more prevalence than female 1.6:1. Nuclear β-catenin immunoreactivitywas detected in 27 (25%) patients of total 109 medulloblastomas; with 11 of them being strong / widespread nucleo-positiveB-catenin (NP) tumors and 17 being a moderate / patchy NP β-catenin tumors, Only in 15 of 27 Medulloblastoma with β-catenin nucleoimmunophenotyping; tissue was available for mutational analysis to find 9 of 15 with CTNNB1 mutations and APC mutations wasn't detected in β-catenin nucleo-positive medulloblastoma. They found an association between good outcome and being β-catenin nucleo-positive medulloblastoma much better than nucleo-negative medulloblastoma; 5 year overall survival (OS) 92.3% (95% CI, 82%-100%) to 65.3%(95% CI, 54.8% -75.7%), and 5 year EFS(PFS) 88.9% (95% CI, 77%-100%) to 59.5% (95% CI, 48.8%-70.2%), 24 children from the 27 were still alive without disease with median follow up period of 7.6 years (4.2 to 11.1 years), and children with LC/A tumors had a more poorer outcome than those with classic type. 4 of the 27 nucleo-positive β-catenin medulloblastoma were LC/A variants but they were still alive, 5 to 10.7 years post diagnosis, 3 of 27 medulloblastomas revealed metastatic disease at presentation, but all the 3 were moderate/patchy β-catenin NP medulloblastoma, all were still alive 7.5 to 10.8 years post diagnosis. this was the 1st study to show an association between nuclear β-catenin immunoreactivity and a favorable outcome in a large uniformly treated cohort of children with non desmoplasticmedulloblastomas. this study was quite specific in their purpose, with clear methods and results but still with few number of cases in the subject of interest, and we could consider it quite old (2005) manuscript but still promising for further studies. Ellison D., et al, (2005)[5].

A retrospective cohort study of 72 medulloblastoma patients who all were operated on in Necker Hospital in Paris, France, with fulfilling all the protocols of consents and ethics in a purpose of proving the efficacy of nucleo-positive β-catenin as a prognostic factor in Wnt pathway tumors, and the association of CTNNB1 with it, For mutational extraction, the standard extraction procedure was done with phenol / chloroform to extract DNA from fresh frozen tumor samples with a blinded histological review for each tumor assessing according to current WHO CNS tumor classification. Immuno-staining for β-catenin was done with a known case with CTNNB1 mutation as a positive control, only in 40 from the total 72 cases had sufficient tissue for RNA extraction for gene expression of Wnt / B-catenin pathway members.

3 patterns of nuclear β-catenin staining were revealed: (A) extensive in 6 cases, (B) focal in 3 cases, and (C) negative in 63 cases, the whole 9 nuclear immunoreactive with 58 of the negative 63, showing cytoplasmic β-catenin expression. With mutational analysis; 6 cases with extensive nucleo-positivety harbored CTNNB1 mutations, while all others were CTNNB1 wild-type. Using Array CGH for genomic profile investigations, no gains of chromosome 17q, or loss of 17p, or whole chromosome 17 gain was detected in the 6 extensive nucleo-positive β-catenin harboring CTNNB1 mutation tumors, 5 of the 6 presented with complete chromosome 6 loss, the other 1 of 6 showed a

whole chromosome 11 gain. On gene ontology categorization, Wnt/β-catenin signaling was the most significant pathway could distinguish both groups of tumors. The mean age of diagnosis of CTNNB1 mutated medulloblastomas was 10.6 years (5.6- 13.2 years) higher than non CTNNB1 harbored tumors 7.1 years, none of CTNNB1 mutated medulloblastoma had metastatic disease at diagnosis, which all of them were of classic histological subtype, their OS was 6.3 years (2.3 -10.1 years) which was longer than in the CTNNB1 wild-type group (5 years OS 53.7%), unfortunately the 3 focal β-catenin nucleo-positive died of the disease within the 1st 3 years from diagnosis, all with classic histology, 2 was local and only one was metastasized. This study has shown that the presence of a CTNNB1 mutation in pediatric medulloblastoma is associated with specific genomic and gene expression profiles, none of the patients with CTNNB1 mutation/ extensive β-catenin immuno-positivity harbored high risk factors, and it is associated with good favorable outcome. Fattet S., et al, (2009)[6].

A retrospective cohort study of 49 CNS PNET and 46 medulloblastomas where immunohistochemical analysis of CTNNB1 and CCND1 was done to demonstrate the status of WNT /B-catenin pathway and cellular localization of CTNNB1. Mutational analysis was done for B-catenin and APC in 22 medulloblastomas where nuclear immunoreactivity was demonstrated in 27% of medulloblastomas. 22 tissue samples of medulloblastoma were obtained from the Cooperative human tissue network (CHTN), 85% were classical, 10% desmoplastic and 5% anaplastic according to WHO criteria.The rest of samples were obtained from the Children's Cancer and Leukemia group (CCLG). The total 46 samples were fixed in 4% phosphate buffered formaldehyde and embedded in paraffin. Immunohistochemistry analysis was done for CTNNB1 where the positive samples are classified according to CTNNB1 location either nuclear (active WNT pathway) or cytoplasmic (inactive WNT pathway). Furthermore, positive nuclear samples were classified according to percentage of positive nuclei in the sample into high (positive nuclei <10%) and low (positive nuclei >10%). Statistical analysis was done using a fisher's exact test for association between clinical factors and immunohistochemical results, Kaplan-Meier method for PFS and OS ratios and Mantel-Cox test for calculation of the differences. Blood samples were also obtained for mutational analysis but none of them contained mutations. The results of the study demonstrated that a lot of factors had a significant effect on the outcome. In patients>5 years, treatment with radiotherapy had a better outcome, patients who relapsed or who had metastasis had worse outcomes. Many samples were classified as unscorable due to necrosis or core loss. Clinical features of differentiation between scorable and unscorable were determined to avoid sampling bias. Of the 46 samples, 37 primary medulloblastomas and one recurrent were scorable and the rest was unscorable. In the medulloblastoma's cohort study, association between B-catenin positive nuclear immunoreactivity and low relapse rate was almost significant of favorable outcome (Fisher's exact test P=0.056) however there was no significant association with progression-free or overall survival (P=0.590, P=0.517 respectively). this might be due to the relatively small sample size (n=37), 5-year overall survival rates for B-catenin nucleo-positive patients was 80% compared with 44% for non B-catenin nucleo-positive patients.

At 10 years, survival rates were 56% for B-catenin nucleo-positive patients and 24% for non B-catenin nucleo-positive patients. Overall survival rates and Kaplan-Meier curves suggested better outcome for Wnt pathway activation in these samples but still there is no significant association. Surprisingly, Wnt pathway activation was associated with poor prognosis in hepatocellular and breast carcinoma. Thus, more investigations have to be done in a larger sample in order to get significant results Rogers H.A., et al, (2009)[11].

4 independent cohorts (n=173) were gathered together (6,14.15) for distinguishing between Wnt / wingless and Sonic Hedgehog (SHH) medulloblastoma subgroups, with Wnt tumors 21(12%) of all 173 cases, all have classic histology, CTNNB1 mutation harbored in 19/20 with one had no available data, with peak incidence in 3-6 year age group.

This study reported the development and validation of minimal diagnostic gene expression signatures which can be routinely applied to identify the different independent medulloblastoma subgroups (SHH, WNT, and non SHH/WNT), to identify RNA extracted from snap-Frozen tumor material, and using different expression assays.

CTNNB1 were identified as the primary pathway activating event present in almost all WNT subgroup tumors, with chromosome 6 losses also affecting the majority of these cases. Schwalbe E., et al, (2011)[13].

4. Discussion

4.1. Conclusions

After comparing the results of reviewing 7 cohort studies, the methods applied to recruiting the patients, gathering data, appropriate ethics committee approval and the authors shown no personal conflicts.

We can't refuse these results for being right or wrong; may be some differences were done due to the methods or protocols of treatment which are considered normal.

The major problem was the relatively small numbers of the nueclo-positive B-catenin medulloblastoma tumors which makes the statistical significance not evident , so we have to apply the UKCCSG/SIOP trial PNET 3, COG ACNS0331 trial and, SJCRH trial SJMB96[7] more wider and in more multi-centres studies to overcome the disadvantage of small numbers of tumor.

All studies considered WNT pathway tumors (β-catenin immunore-active medulloblastoma) as a low risk tumor in

the absence of high-risk factors: clinical (M+ status), pathological (LC/A variant), and molecular (MYC amplification) factors. The special nature of the WNT tumor as shown by its restricted range of age at presentation, its pathological and cytogenetic associations, and its relatively good outcome; all are aligned with considering it distinctive from other types of medulloblastomas[1,3,4,5,11,13].

Also it was obvious that extensive nucleo-positive β-catenin medulloblastoma is better than focal nucleo-positive ones, while nucleo-negative ones or even cytoplasmic immunoreactive tumors don't have good prognosis or outcome as the first one mentioned[6].

CTNNB1 is now for sure known to be associated with extensive nucleo-positive β-catenin medulloblastoma but still its rule is quite unknown[3,4,5,6], also Monosomy 6 chromosomes were associated with extensive nucleo-positive β-catenin in most of the cases, but none of CTNNB1 mutations, Monosomy 6, and any mutations associated had a better outcome than being only nucleo-positive β-catenin medulloblastoma[3,4].

None of chromosome 17 defects were found to have any relation or association with β-catenin/ Wnt pathway medulloblastoma tumors[3,4,5,6].

Studies have revealed good outcome for WNT tumors with standard adjuvant therapy[3,6] so we can have the courage to try modulating the treatment protocol for seeking better results.

Also it is still vague; is the best outcome of β-catenin nucleo-positive patients harboring CTNNB1 mutations related to the less invasiveness or an increased response to therapy?[6]

Salaroli R, et al (2008)[12] has made the first big step of applying the result of what we got and put it in a real application, when he studied the effect of nucleo-positive β-catenin in Wnt pathway tumors to see its response to Gamma radiation, it's still in the first steps and we still can't judge but we have to seek for an application like this, hoping to reach the goal of a cure for all medulloblastoma in 2035[7] .

4.2. Recommendations

1. Doing more studies to know the real rule of β-catenin, CTNNB1 mutations, Monosomy 6, APC, and any associations with Wnt/wg pathway medulloblastoma tumors.
2. Applying the multi institutional studies more and even makes it international to overcome the defect in patients' numbers.
3. Doing more research on the new classification of medulloblastomas as a High, Standard, and Low risk tumors according to risk stratification factors and get use of it in treatment protocols' application to get the best outcome, and reduce the adverse effects of long term adjuvant therapy.

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Abbreviations

ar-CGH= array-comparative genomic hybridization
FFPE =formalin fixed paraffin embedded tissue
LC/A=large cell/ anaplastic
OS =overall survival
PFS =progression free survival =EFS= event free survival
FISH =fluorescence in situ hybridization

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