Review of Karyotypic Data from Low Grade Glial Brain Tumors, Specifically Pilocytic Astrocytomas, and Correlation of Genetic Aberrations with Tumor Recurrence.

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Review of karyotypic data from low grade glial brain tumors, specifically pilocytic astrocytomas, and correlation of genetic aberrations with tumor recurrence.

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Abstract: Brain tumors are the most common solid tumor of childhood. Approximately 50% of pediatric CNS tumors are low grade gliomas (WHO grade I or II) and Pilocytic astrocytoma (PA) is the most common accounting for 33% of all gliomas in children 0-14 years and ~18% of all childhood brain tumors. Prognosis with this slow-growing tumor is excellent; 10 year overall survival of ~95%. However, event free survival averages ~50%. Patient age and extent of tumor resection are key prognostic factors; tumor location and size impact resection and outcome. Histopathological features indicate PA is a benign tumor and rarely are anaplastic features of malignancy present.

This study sought to determine if chromosomal aberrations correlate with increased risk of tumor recurrence. Observation shows that while the majority of PA have a normal karyotype, a portion have highly aberrant karyotypes; the clinical significance of which is unclear.

Methods: Pathology archives were queried for PA between mid-2008 and mid-2017. Review included chromosome, FISH, microarray, molecular results, cytogenetic methods, histopathology, tumor location, patient age, extent of surgical resection, chemotherapy, radiotherapy, and outcome. Karyotypes were defined as “aberrant” if there were multiple bizarre chromosome abnormalities, multiple telomeric association (tas) figures or translocations, or multiple dicentric chromosomes. Routine cell culture methods were used with mechanical +/- enzymatic disaggregation, alpha-MEM medium, and monolayer covERSHEY cultures with harvest as soon as feasible to capture metaphase cells.

Results: Of 64 cultured PA, 4 failed to grow. Karyotypes were normal (n=32), simple (n=3), hyperdiploid (n=12), or aberrant (n=13). Four patients had a second tumor resection; 2 had aberrant and 2 had normal karyotypes on the initial and repeat studies. Of the 13 patient tumors with aberrant karyotypes, 6 tumors (CMH cases 1-5) demonstrated tas, dicentrics, subclones, etc., and two (CMH cases 6, 7) had multiple cells with an excess of aberrant chromosomes. Four tumors (CMH cases 8-13 – not shown) had a normal karyotype with one or two highly aberrant cells; of these, one patient with two resections (CMH cases 11 & 12) showed two highly aberrant cells on both the initial and second study.

Discussion: Highly aberrant karyotypes are unexpected in benign tumors. PA is a histologically benign tumor with ~95% 10 year overall survival. Repeatedly finding highly aberrant karyotypes in some of these tumors begs the question of clinical significance. How should these karyotypes be interpreted? Finding the abnormalities in tumors resected twice suggests an ongoing cellular/biologic process specific to that tumor tissue. The repeat finding of tas and dicentrics suggests a role for telomere dysfunction in these tumors. This is consistent with up-regulation of TRF1 and TRF2 (TTAGGG repeat-binding factors) occurring in the early stages of LGG carcinogenesis, which is characterized by short telomeres, genomic instability, low proliferative rate and prolonged life span (1).

Limitations of the study: Data are limited – few patients, inconsistent FISH, microarray and molecular studies were done; no sequence analysis. Multiple factors play a role in patient outcome including tumor location and resectability.

Conclusions: Additional cases, additional follow-up, additional genomic analyses are needed. Next step: WES of rearranged cases is planned.

<table>
<thead>
<tr>
<th>Age</th>
<th>Rejection; Location</th>
<th>Outcome</th>
<th>Karyotype</th>
<th>Microarray / FISH result</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.5y M</td>
<td>Subtotal; Suprasellar, 3rd ventricle, midline</td>
<td>Residual tumor; History of ADHD</td>
<td>46,XY; 46,XY[2]</td>
<td>Microarray - normal FISH - +</td>
</tr>
<tr>
<td>10y F</td>
<td>GTR; Basal ganglia, Right, parietal lobe</td>
<td>No residual tumor at 6 mo post surgery; Homonymous hemianopsia</td>
<td>46,XY+2, +5,5,5</td>
<td>Microarray - 7q24 dup; FISH - +7 with 7p34 dup2</td>
</tr>
<tr>
<td>9y M</td>
<td>GTR; Cerebelum, midline</td>
<td>6-7 post surgery doing well; History of autism, ADHD</td>
<td>46-48,XY+5, +6, +11, +14, 22,p, p13, p13</td>
<td>nd</td>
</tr>
<tr>
<td>5.5y M</td>
<td>Subtotal; Diencephalon, suprasellar, optic system, midline</td>
<td>Tumor regrowth; chemo tumor growth -&gt; XRT; Neurological sequela, alive, stable</td>
<td>47,XY; +7, +14,22</td>
<td>nd</td>
</tr>
<tr>
<td>10.5y M</td>
<td>GTR; Cerebelum, midline</td>
<td>Residual tumor</td>
<td>46-48,XY+5, +6, +11, +14, 22,p, p13</td>
<td>FISH - BRAF no dup</td>
</tr>
<tr>
<td>13.6y M</td>
<td>GTR; re-resection; Cerebelum, midline</td>
<td>Residual tumor; 4th ventricle outlet obstruction</td>
<td>55,XXY, +7, +15, +16, +20</td>
<td>nd</td>
</tr>
<tr>
<td>16.5y M</td>
<td>Partial resection; Cerebelum, midline</td>
<td>Residual tumor; Prolonged rehab</td>
<td>46,XY[1]</td>
<td>Microarray - normal</td>
</tr>
<tr>
<td>15y F</td>
<td>GTR; Hypothalamus, midline</td>
<td>No residual tumor at 1yr post 64-69 chromosomes with exessive rearrangements</td>
<td>47,XY; +7</td>
<td>Microarray - +7, 7q34 dup</td>
</tr>
</tbody>
</table>