**Title**: Diffuse Glioneuronal Tumor with Oligodendroglioma-like Features and Nuclear Clusters (DGONC) – A Novel Pediatric Brain Tumor Entity

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**Background**: Epigenomic analysis has emerged as a tool that enables profiling of oncogenic lineages of different brain tumors and provides improved sub-classification of existing tumor entities\(^1\). Diffuse Glioneuronal tumor with Oligodendroglioma-like features and Nuclear Clusters (DGONC) is a newly proposed provisional neuroepithelial tumor type described by World Health Organization (WHO)\(^2\) which requires methylome profiling for clinical diagnosis. Available literature suggests DGONC is most prevalent in the pediatric population without brain regional predilection\(^3\). These rare cases show consistent monosomy of chromosome 14 and frequent histological presentation of perinuclear haloes and nuclear clusters. Here we report a DGONC case suspected on histomorphologic examination and confirmed by methylation profiling\(^2\)–\(^4\).

**Clinical History**: This 15 year-old previously healthy male presented with two months of frequent seizures, characterized by impaired awareness with variable emesis, tinnitus, jaw locking, lip smacking, and secondary generalization. His verbal memory had also subjectively declined. Electroencephalogram (EEG) revealed spike and sharp discharges as well as subclinical seizures in the left temporal region. Brain MRI showed a 2.3 x 2.0 x 1.7 cm non-enhancing space-occupying lesion in the left mesial temporal lobe with regional mass effect upon the amygdala and hippocampus (Fig. A). The initial differential diagnosis included low-grade glioma, ganglioglioma, and focal cortical dysplasia. The lesion was resected using a transcortical approach (Fig. B). The final pathologic diagnosis was established on the resected specimen.

**Figure A**: MR image showing a space-occupying lesion (pointed by the arrow) in the left mesial temporal region. Scale bar = 2.0 cm.

**Figure B**: Intra-operative image showing gross appearance of the lesion in vivo (pointed by the arrow). The white vascular structure that situates superior to the lesion is the hippocampus.

**Case Findings**: The tumor was moderately cellular and composed of sheets of monotonous cells with round nuclei and scant cytoplasm (Fig. C). A few nuclear clusters and entrapped cortical neurons were present (Fig. D). Rare perinuclear clearing, an oligodendroglioma-like feature, was seen (Fig. E). Tumor cells were diffusely positive for Olig2 (Fig. F) and negative for GFAP (which highlighted entrapped reactive astrocytes). ATRX was retained. Neither overexpression of p53 nor IDH1-R132H mutation were identified by immunostaining. Only rare mitotic figures were present, and the Ki-67 proliferation index was approximately 3-4 %. The constellation of features was suggestive of a low-grade glial/glioneuronal tumor, and a diagnosis of DGONC was favored. Next generation sequencing revealed loss of one copy of chromosome 14. No other pathogenic variants were identified. The specimen was further evaluated by methylation profiling performed at the National Institute of Health (NIH), and the classifier confirmed the diagnosis of DGONC with a high confidence score. Of note, in the most recent WHO guidelines, DGONC is characterized by common oligodendroglioma-like histological features, nuclear clusters, and occasional neuronal differentiation\(^2\). While our case contained small cells with round nuclei and occasional nuclear clusters, perinuclear haloes and definitive neuronal differentiation were not present. Additionally, the previously described micro- or macro-calcifications and vascular proliferation\(^2\),\(^4\) were also not found by histology or imaging.
Discussion and Conclusion: DGONC is a new entity that was first differentiated and classified by its distinct DNA methylation profile. Immunohistochemical, morphological, and other genetic features were subsequently surveyed on limited available specimens for further characterization. A total of 34 cases (predominantly in the pediatric population) have been reported to date. While the convergent characteristics of DGONC include monosomy 14 and frequent presence of perinuclear haloes and nuclear clusters, the absence of these features does not entirely rule out the DGONC diagnosis. Histologic features of DGONC can mimic low-grade entities such as oligodendroglioma, neurocytoma, and ependymoma as well as high-grade entities including anaplastic oligodendroglioma and primitive neuroectodermal tumors. Improved histomorphological characterization has been limited by the paucity of cases and should be pursued as more cases are identified through methylation profiling. Notably, DGONC shares morphological features and methylation profile spatial proximity with CNS neuroblastoma. Consistent loss of chromosome 14 heterozygosity has been previously identified in neuroblastoma, a finding similar to monosomy 14 found in DGONC. It is hypothesized that loss of tumor suppressor genes on 14q contributes to the tumorigenesis of neuroblastoma. Combined epigenomic and genomic analyses focusing on chromosome 14 will permit exploration of both disease entities’ pathogenesis and testing the hypothesis that DGONC and CNS neuroblastoma may be two sub-categories of CNS embryonal tumor.

References: