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OCCURRENCE OF ANAPLASTIC OLIGODENDROGLIOMA IN A PATIENT WITH WILLIAMS SYNDROME: A CASE REPORT WITH ANALYSIS OF MUTATIONAL PROFILE OF TUMOR

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ABSTRACT
Williams syndrome is a rare congenital developmental disorder characterized by a constellation of distinctive facial dysmorphisms, mental retardation, cardiovascular anomalies, infantile hypercalcemia, delayed developmental milestones, dental and musculoskeletal anomalies and distinctive personality traits. A majority of patients with Williams syndrome exhibit a hemizygous micro-deletion of chromosome 7q11.23, which is the locus of some 20-30 genes including the ELN gene that encodes the structural protein elastin. Chromosome 7q contains putative tumor suppressor genes and is one of the chromosomes that are frequently involved in chromosomal aberrations in human malignancies. A paucity of tumors (three) has been reported in the literature to occur in patients with Williams syndrome. We report a case of anaplastic oligodendroglioma that occurred in a 31-year-old man with Williams syndrome. Mutational profiling by loss of heterozygosity analysis using a panel of polymorphic micro-satellite markers indicated combined deletion of chromosome 1p and 19q. We draw attention to this apparently rare or possibly under-reported occurrence of tumors in patients with Williams syndrome and suggest that Central Nervous System [CNS] tumors be considered as differential diagnoses in such patients when they present with unanticipated neurologic symptoms that are not attributable to those commonly associated with Williams syndrome.

Keywords: Williams's syndrome, anaplastic oligodendroglioma, loss of heterozygosity

INTRODUCTION
Williams syndrome is a rare congenital developmental disorder with an estimated worldwide incidence of 1 in 20,000 to 1 in 50,000 births [1,2,3,4] It is characterized by a constellation of distinctive facial dysmorphisms, mental retardation, cardiovascular anomalies, infantile hypercalcemia, delayed developmental milestones, dental and musculoskeletal anomalies and distinctive personality traits. When it was first described as a distinct entity in 1961 by J.C.P. Williams[5] Williams syndrome consisted of supravalvular aortic stenosis, mental retardation and a characteristic "elfin" facies. Beuren's description followed a year later, and reinforced Williams' original observations, with the addition of dental anomalies, peripheral pulmonary artery stenosis and excessive sociality as components of the syndrome [6, 7].Since that time, the list of symptoms and phenotypic features identified as occurring at higher frequencies in individuals with Williams Syndrome has continually expanded [4,8], (Table 1). The majority of affected individuals are now recognized to have hemizygous micro-deletion of chromosomal locus 7q11.23, which exhibits an autosomal dominant mode of inheritance but is more commonly acquired from sporadic germ-line mutations, typically an uneven meiotic recombination of chromosome 7 homologues [9,10]. This genotype is readily demonstrated by Fluorescent In-situ Hybridization [FISH] analysis for confirmatory diagnostic purposes [9]. The deletion includes, most notably, the ELN gene, which encodes for the structural protein elastin, large quantities of which are found in lungs, intestine, skin and arterial walls. The subsequent deficiency of elastin is responsible for the multitude of connective tissue abnormalities found in the syndrome. Indeed, it is the deficiency of elastin in arterial walls that leads to the most clinically significant manifestation of Williams Syndrome, supravalvular aortic stenosis and peripheral pulmonary stenosis, estimated to affect 75% of individuals [11] Bellugi et al [12] suggested that anomalous development of specific cerebral subsystems occurs in Williams syndrome and are reflected in gross cerebral dysmorphologies. These may include dorsal brain anomalies, decreased myelination, decreased parieto-occipital volumes and microcephaly. Although the brain volume is diminished to 80% of normal in Williams Syndrome, frontal lobe sand limbic regions of the temporal lobes are generally preserved, as is the neocerebellum [3,12,13,]. The neocortical cytoarchitecture has been described to be normal [13]. Alzheimer's disease-like pathology with neurofibrillary tangles and BA4 Amyloid

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plaques in the neocortex and mesial temporal lobe has been reported in a 35-year-old man with Williams syndrome [14]. Despite this plethora of CNS abnormalities, only one case of a CNS neoplasm has been reported to occur in a patient with Williams syndrome. In their report, Semmekrot et al[4] described the occurrence of a low grade astrocytoma in a 5-year-old bony who had presented with non-pathognomonic symptoms of headaches, left-sided hemiparesis, deterioration of vision and progressive dysarthria.We report the second case of a glioma (anaplastic oligodendroglioma) occurring in a 31-year-old white male with Williams syndrome who had presented with acute behavioral changes. This tumor was subjected to molecular examination by loss of heterozygosity analysis using a panel of polymorphic micro-satellite markers. This case illustrates the mutational profile of a glioma occurring in the setting of Williams syndrome and suggests that CNS neoplasms may be considered as differential diagnoses in patients with Williams syndrome who present with CNS symptoms that are distinct from baseline symptoms [11]. We draw attention to the occurrence of gliomas in Williams syndrome since chromosome 7 is one of the chromosomes that are frequently involved in chromosomal aberrations observed in human malignancies [15].

CASE REPORT

Our patient is a 31-year-old mentally retarded Caucasian man diagnosed with Williams syndrome at one year of age. At that time, he presented with failure to thrive and significantly delayed developmental milestones. His parents described his childhood and early adulthood to be relatively healthy except for hypercalcemia, which had resolved during the early years of his life. He worked as a volunteer in a local railroad museum. Approximately 4 weeks prior to presentation, his parents noted an acute change in his mood. Described as usually extremely cheerful, friendly and cooperative, he had begun to appear increasingly depressed, withdrawn, combative and emotionally labile with protracted crying spells. In addition, he appeared confused and was often unable to make simple decisions. Subsequent physical examination and neurologic evaluation by his primary care physician revealed no abnormalities. Brain MRI revealed a fairly well circumscribed, large heterogeneously enhancing left posterior parietal mass that showed focal calcification (Figure 1) accompanied by surrounding edema with mass effect. At this point the patient was referred to our institution.Upon admission, physical examination revealed an alert and well-oriented man who, although very anxious and tearful, appeared to be in no physical distress. Physical examination especially of the central and peripheral nervous system was unremarkable. The patient underwent left parietal craniotomy and gross total resection of the left Parietal mass by neuro-navigational guided microsurgery. Neuropathologic examination indicated Anaplastic Oligodendroglioma (W.H.O. Grade III/IV). Recovery was uneventful except for mild residual, right upper extremity weakness and a mild disturbance in gait, both of which rapidly improved. He continued to experience emotional lability with long episodes of crying. The patient received a full course of postoperative radiation therapy to the tumor bed comprising 6000 cGY in 30 fractions using the 6 MV photo beam which was followed by chemotherapy with procarbazine and lomustine (1-{choloroehyl}-3-cyclohexyl-1-nitrsourea). At 12 months follow-up he did not have any residual deficit. Serial brain MRI with and without gadolinium revealed abnormal signal in the left parietal lobe consistent with postoperative changes without any evidence of no intervals change or tumor recurrence.

Neuropathologic Examination:

Microscopic examination revealed a high-grade glial tumor with oligodendroglial differentiation. The tumor exhibited a hypercellular, polymorphous architecture comprising areas with solid sheets of cell admixed with dense networks of branching capillaries, microcystic areas and honeycomb areas. The neoplastic cells were hyperchromatic and mildly pleomorphic comprising round to oval cells with rounded enlarged nuclei, scattered nucleoli and scant cytoplasm. Microcystic and mucoid areas were present (Figure 2). In many foci, the characteristic peri-nuclear cytoplasmic clearing of swollen cells forming a honeycomb appearance was noted. Numerous mini-gemistocytes were present and mitotic figures were frequently encountered. Focal necrosis without nuclear pseudopalisading was noted. Focal microcalcification and microvascular proliferation were present. The Ki-67 proliferation was calculated as 19.4% using the protocol reported by Pollack et al [16].

Molecular Examination:

The profile of mutational/chromosomal alterations of this tumor was studied for allelic loss of heterozygosity (LOH) at chromosomal loci containing putative tumor suppressor genes according to Knudson's hypothesis of tumorigenesis [17] (Table2). LOH studies were performed by standard PCR amplification of tumor DNA extracted from microdissected targets of unstained 4-micron thick sections of paraffin-embedded and formalin fixed tissue as has been previously reported by Finkelstein et al [18] and Rolston et al [19]. A panel of thirteen fluorescent-labeled primer pairs was used for the amplification of micro-satellites situated in close proximity to known or putative suppressor genes such as PTEN and p53. LOH was determined by the relative intensity of polymorphic capillary electrophorectic allelic bands.

Table 1: **Possible Clinical Criteria for the Diagnosis of Williams Syndrome.**

Supravalvular Aortic Stenosis	**Mental Retardation**
Other arterial stenosis	'Cocktail-party' personality
Hypertension	Friendly
Typical facies	Always happy
Broad Forehead	Loquacious
Medical eyebrow flare	Charming
Short palpebral fissures	Impaired visual-spatial ability
Hypotelorism	Relatively preserved language
Depressed nasal bridge	Preserved face processing
Epicanthal folds	Infantile hypotonia
Periorbital fullness	Wide gait and in-coordination
Strabismus	Dolichocephaly
Blue eyes and stellate iris	Chiari I malformation
Anteverted nares	
Hyperacusis	
Long philtrum	Anxiety and attention disorders
Full prominent lips	Deep, low and heavy voice
Wide open mouth	Pre and postnatal growth deficiency
Molar hypoplasia and widely spaced	Microcephaly
Teeth Small penis	
Hallux valgus	Pectus excavatum
Hypoplastic nails	Inguinal and umbilical hernia
Fifth finger clinodactyly	

Table 2: **Genotypic Profile of Tumor As Determined By Micro-Satellite Analysis for Loss of Heterozygosity (LOH)**

	Panel Of Micro-Satellite Markers										
Tissue Target	**Ip32 DIS-407**	**Ip34 MYCL**	**Ip34 DIS-1193**	**9p21 D9S-254**	**9p21 D9S-251**	**10q23 D10S-520**	**10q23 D10S-1173**	**17p13 D17S-1289**	**17p13 D17S-974**	**19q D19S-400**	**19q D19S-559**
N-1	I	I	NI	NI	NI	I	I	I	NI	I	I
T-1	LOH	LOH	NI	NI	NI	NO LOH	NO LOH	NO LOH	NI	LOH	LOH
T-2	LOH	LOH	NI	NI	NI	NO LOH	NO LOH	NO LOH	NI	LOH	LOH

N-1: Micro-dissected non-neoplastic brain tissue to determine constitutional allelic heterozygosity at chromosomal locus.
T-1: Area 1 of micro-dissected tumor
T-2: Areas 2 of micro-dissected tumor
I: Informative (presence of heterozygous alleles), NI: Non-informative (homozygous alleles, LOH: Loss of heterozygosity, NO LOH: No loss of heterozygosity

This anaplastic oligodendroglioma showed combined chromosomal deletion (LOH) of both the short arm chromosome 1 (1p) and the long arm of chromosome 19 (19q) (Table 2). DNA extraction and PCR amplification using micro-satellite primers for chromosomes 7q (D7s1530 and D7s460) failed after three runs and remains inconclusive.

Table 3: **Some Putative Genes That May Account For the Neurobehavioral Phenotype of Williams Syndrome.**

Gene	**Gene Product**
LIMK1	Tyrosine kinase, axon guidance and growth cone formation
STX1A	Syntaxin 1A, neurotransmitter release
FZD3	Brain development and cell differentiation
FKBP6	Immunophilin FK-506 binding protein

DISCUSSION

The origin of connective tissue anomalies, as is seen in Williams syndrome, has been explained by the deletion of the ELN gene locus on chromosome 7q, which results in haplo-insufficiency of elastin. The unique cognitive and behavioral phenotype of Williams syndrome can be possibly ascribed to the inclusive deletion of some 20-30 genes that are contiguous to the ELN gene in this region that spans approximately 1.5 MB. Many of these genes are expressed in the brain and perform major roles in brain development and/or signal transmission [3, 10]. Some of these genes and their putative roles are listed in Table 3. Chromosomes 7 contains putative tumor suppressor genes and is one of the genomic regions that are frequently involved in chromosomal aberrations observed in human malignancies. Neoplasms have reported in individuals with constitutional cytogenetic anomalies involving chromosome [715.] Hasle et al [15] reviewed the occurrence of cancers over a period of 50 years in a cohort of 183 individuals in Denmark with constitutional chromosome 7 abnormalities. This cohort included 16 individuals with microdeletion of the 7q11.23 locus confirmed by in situ hybridization. They reported no increase in the overall risk of developing cancers in their study cohort but some strong selection biases were evident in their methods. It is obviously not possible to know if the glioma arising in our patient represents a sporadic co-incidental event or if it represents a direct consequence of the genetic abnormalities associated with William's syndrome. Only three cases of neoplasm and malignancies have been reported in patients with Williams syndrome [del(7)(q11.23q11.23)] including an astrocytoma [4], a Non-Hodgkin's lymphoma [1] and a mucinous cystadenoma of the ovary [20].Although there has not been any report on the mutational profiles of gliomas that occur with Williams syndrome, the mutational profile of this case, as evinced by combined deletion of chromosomes 1p and 19q, suggest a better prognosis of our patient. It has been demonstrated repeatedly that combined deletion of chromosomes 1p and 19q are specifically strong predictors of chemotherapeutic response and prolonged overall survival in anaplastic oligodendroglioma treated with PCV chemotherapy [21,22,23]

In summary the purpose of this article is to draw attention to this apparently rare and possibly under-reported occurrence of a glioma in patients with Williams syndrome. When CNS symptoms occur, other possible causes of illness other than those commonly attributed to William's syndrome should be considered. Further studies are required to find out if individuals with Williams are predisposed to malignancies since chromosome 7q which contains putative tumor suppressor genes is micro-deleted in Williams syndrome.

REFERENCES

1. **Felice P, Ritter S, Anto J.** Occurrence of non-Hodgkin's lymphoma in Williams syndrome-case report. Angiology, 1994;45(2):167-170

2. **Jones KL,** Williams syndrome: an historical perspective of its evolution, natural history, and etiology. Am J Med Gen 1990;6:89-96

3. **Lenhoff HM, Wang PP, Greenberg F, Bellugi U**. Williams syndrome and the brain. Sci Amer 1997;277:68-73.

4. **Semmekrot BA, Rotteveel JJ, Bakker-Niezen SH, vd Logt F.** Occurrence of an astrocytoma in a patient with Williams syndrome. Pediat Neurosci 1986;12:188-191.

5. **Williams JCP, Barrat-Boyes BJ, Lowe JB**. Supravalvular aortic stenosis. Circulation 1961;24: 1311-1318

6. **Beuren AJ, Apitz J, Harmjanz, D.** Supravalvular aortic stenosis in association with mental retardation and a certain facial appearance. Circulation 26: 1235-1240

7. **Beuren AJ, Schulze C, Eberle P, Harmjanz D, Apitz J.** The syndrome of supraclavicular aortic stenosis, peripheral pulmonary stenosis, mental retardation and similar facial appearance. Am J Cardiol 1965; 13:471-483.

8. **Jones KL. Dysmorphology. In: Behrman Re, Kliegman RM, Jenson HB,** eds. *Nelson Textbook of Pediatrics*. 16th ed. Philadelphia PA: W.B. Saunders Company; 2005:535-538.

9. **Borg I, Delhanty JD, Baraitser M**. Detection of hemizygosity at the elastin locus by FISH analysis as a diagnostic test in both classical and atypical cases of Williams syndrome. J Med Genet 32; 692-696.

10. **Schmitt J.** Williams syndrome: recent developments. Current Opinion in Psychiatry 2001; 14(5):451-456.

11. **Metacalfe K.** Williams syndrome: an update on clinical and molecular aspects. Arch Dis Child 1999; 81(3): 198-200

12. **Bellugi U, Bihrle A,** Neville H, Doherty S. Neuropsychological, neurologic and neuroanatomical profile of Williams syndrome. Am J Med Gen 1990;suppl 6:115-125.

13. **Francke U.** Williams-Beuren syndrome: genes and mechanisms. Hum Mol Gen 1999;8:1947-1954.

14. **Golden JA, Nielsen GP, Pober BR, Hyman BT**. The neuropathology of Williams syndrome: report of a 35-year-old man with presenile beta/A4 amyloid plaques and neurofibrillary tangles. Arch Neurol 1995;52: 209-212.

15. **Hasle H, Olsen J, Hanse J et al.** Occurrence of cancer in a cohort of 183 persons with constitutional chromosome 7 abnormalities. Cancer Genet Cytogent. 1998;105:39-42.

16. **Pollock IF, Campbell JW, Hamilton RL, Martinez AJ, Bozik ME.** Proliferation index as a predictor of prognosis in malignant gliomas of childhood. Cancer 75:849-856, 1996.

17. **Knudson AG.** Genetics and etiology of human cancer. Advances in Human Genetics. 8:1-66, 1977.

18. **Finkelstein SD, Przgodzki RM, Pricolo VE, Sakallah SM, Swalsky PA, Bakker A, Lanning R, Bland KL, Cooper Dl.** Prediction of biological aggressiveness in colorectal cancer by p53/K-ras-2 topographic genotyping. Mol. Diagn 1996;1:5-28.

19. **Rolston R, Sasatomi E, Hunt J, Swalsky PA, Finkelstein SD**. Distinguishing de Novo Second Cancer Formation from Tumor Recurrence: Mutational Fingerprinting by Microdissection Genotyping J Mol Diagn 2001;3:129-132.

20. **Marles S, Goldberg N, Chudley A.** Mucinous cystadenoma of ovary in a patient with Williams syndrome. Am J Med Genet. 1993;46(3):349.

21. **Cairncross JG, Keisuke U, Zlatescu MC et al**. Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas. *J Natl Cancer Inst.* 1998;90(19):1473-1479.

22. **Ino Y,Betensky RA, Zlatescu MC et al.** Molecular subtypes of anaplastic oligodendroglioma: implications for patient management at diagnosis. Clin Cancer Res 2001:7: 839-845

23. **Smith JS, Perry A, Borell TJ et al.** Alterations of chromosomes arms 1p and 19q as predictors of survival in oligodendrogliomas, astrocytomas and mixed oligoastrocystomas. J of Clin Oncol. 2000;18(3):636-645.