

WAGR Syndrome – A case report

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ABSTRACT

The WAGR syndrome is a multiple congenital anomaly–mental retardation syndrome caused by interstitial deletion of the distal portion of chromosome 11p13. It is a contiguous gene deletion syndrome, and WAGR is an acronym for the primary features: W for Wilms tumor, A for aniridia, G for genital anomalies, and R for mental retardation. Wilms tumor and male genital anomalies are caused by deletion of the WT1 tumor-suppressor gene, and aniridia is caused by deletion of PAX6 ocular developmental gene. Mental retardation is presumed to be a consequence of deletion of multiple as yet unidentified genes in the region. Individuals with the WAGR syndrome have a high risk for developing Wilms tumor and late-onset renal failure, and should be monitored for these complications.

Keywords: Wilms tumor, aniridia, genitourinary malformations, mental retardation.

A one year old boy presented in our institution with the complaints of delay in development milestones. On thorough examination he was found to have aniridia, Wilms tumor, undescended testis and mental retardation. The observation that aniridia is associated with Wilms tumor led us to believe that the findings were consistent with WAGR syndrome. Miller first described the association of aniridia, hemihypertrophy, and other congenital anomalies with Wilms tumor. The syndrome subsequently became known as the WAGR syndrome. The WAGR syndrome is one of the best-studied 'contiguous gene syndromes'. The incidence of WAGR syndrome has not been determined and there are no consensus diagnostic criteria for WAGR syndrome. Given the widespread expression of the PAX6 gene in the central nervous system, there is a surprising paucity of neurological abnormalities reported in individuals with WAGR syndrome, other than mental retardation.

CASE REPORT

The child was brought with the history delay in development as observed by the mother with inability to move left limbs and lump in left side of abdomen. Physical examination revealed facial dysmorphism, aniridia (but the degree of vision loss could not be assessed), a palpable mass located in the left flank; immobile on respiration and bilateral undescended testis. Determining the degree of retardation was impossible however delay in developmental milestones were observed. The mother's pregnancy and the patient's birth history were generally unremarkable and family history was not contributory.

Routine blood investigations showed no abnormalities. Abdominal US detected an echogenic mass lesion measuring 48 X 44 X 52 mms in the inferior pole of the left kidney, 12 mm lymph node in left iliac region and bilateral undescended testis located at deep inguinal ring.

Contrast enhanced CT revealed a Large lesion measuring approximately 56 X 58 mms with central areas of necrosis and surrounding solid areas involving the inferior and mid poles of the left kidney with thin peripheral rim of contrast enhancement – suggestive of Wilms Tumor. A small lipomatous lesion in the right intradural aspect of the spinal cord adjacent to the cord in lower thoracic region was also detected. Bilateral undescended testis with right testis located in the superficial part of deep inguinal ring and left testis in the region of deep inguinal ring and spina bifida of the lower lumbar vertebrae were also noted [Fig.1-3].

Contrast enhanced CT of brain revealed a large cystic area in the right temporal area with poorly visualised posterior cortical matter and poorly separated from the right sylvian fissure, dilated right frontal horn, temporal horn, trigone and body of right lateral ventricle with regression of right frontal lobe and enlarged CSF space adjacent to it. Gyral enhancement in right parieto-occipital region was suggestive of angiomas [Fig.4-6].

DISCUSSION

The observation that aniridia is associated with Wilms tumor was made 50 years ago and confirmed 11 years later by Miller *et al.* In 1978, interstitial deletion of chromosome band 11p13 was reported in 3 individuals, and hence the WAGR syndrome (W for Wilms tumor, A for aniridia, G for genital anomalies, and R for mental retardation) was proven to be a chromosomal microdeletion syndrome.¹ The association is aniridia, GU malformations, and mental retardation (AGR) syndrome if Wilms tumor is absent and Wilms tumor, aniridia, GU malformations, and mental retardation (WAGR) syndrome if Wilms tumor is present.

Patients with an unusual complex of congenital developmental abnormalities such as aniridia, genitourinary (GU) malformations, and mental retardation are at high (>30%) risk of having a Wilms tumor. As late-onset nephropathy is now recognized as a long-term complication of the WAGR syndrome,² individuals with sporadic aniridia and nephropathy should be considered highly likely to have the syndrome.

The seminal discovery that WAGR syndrome is caused by deletion of band 11p13 led to identification of the *WT1* tumor-suppressor gene^{3,4} and the *PAX6* ocular developmental gene⁵ in the region. Hence, WAGR is a classical contiguous gene deletion syndrome, whereby the phenotype is caused by deletion of several neighboring genes in the region.

WAGR syndrome affects the development of seemingly disparate areas of the body, including the kidney, the GU system, the iris of the eye, and the central nervous system (CNS).

The constitutional loss of one allele of the Wilms tumor suppressor gene (*WT1*) results in GU anomalies and forms the first of 2 genetic events in the development of a Wilms tumor. Alterations to the remaining allele result in the development of a Wilms tumor, usually in early childhood. Meanwhile, the deletion of one copy of the *PAX6* gene is responsible for aniridia. The exact cause of mental retardation in these patients remains to be explained.

The precise risk for Wilms tumor in children with WAGR syndrome is not known, but Turleau's original estimate of about 30.0% is still cited in the literature.⁶

Most individuals with the WAGR syndrome will have moderate to severe visual impairment, due to the pan ocular effects of deletion of one copy of the *PAX6* aniridia gene. The aniridia, or iris hypoplasia, per se can cause photophobia. However, significant visual loss occurs due to a combination of any or all of the following: foveal hypoplasia, optic nerve hypoplasia, cataract, corneal pannus, subluxation of the lens, and secondary glaucoma.⁷

A large spectrum of GU abnormalities is associated with WAGR syndrome; these include cryptorchidism, hypospadias, and renal and ureteral malformations. The presence of pseudohermaphroditism should alert the clinician to the possibility of Denys-Drash syndrome, a distinct diagnosis resulting from constitutional *WT1* mutations.

Genital anomalies are usually present in males, presenting typically as cryptorchidism, hypospadias, small penis, and/or hypoplastic scrotum. While there are no reports of female external genital anomalies, a variety of internal genital anomalies, including streak gonads, uterine malformation (hypoplastic vs. unicornuate), and absent uterus and ovaries have been observed in females.^{8,9}

The range of cognitive impairment is quite wide, from normal functioning in a few individuals to more severe mental retardation in the majority.⁸ The cognitive function of patients with WAGR syndrome is highly variable. The appearance of retardation is correlated with the amount and position of genetic material lost from chromosome 11. Cognitive testing must be performed carefully and is more difficult to evaluate in children with vision loss.

REFERENCES

1. Riccardi V, Sujansky E, Smith AC, Francke U. Chromosomal imbalance in the Aniridia-Wilms' tumor association: 11p interstitial deletion. *Pediatrics* 1978; 61: 604-10.
2. Breslow NE, Takashima JR, Ritchey ML, Strong LC, Green DM. Renal failure in the Denys-Drash and Wilms' tumor-aniridia syndromes. *Cancer Res* 2000; 60: 4030-32.
3. Call KM, Glaser T, Ito CY *et al.* Isolation and characterization of a zinc finger polypeptide gene at the human chromosome 11 Wilms' tumor locus. *Cell* 1990; 60: 509-20.
4. Gessler M, Poustka A, Cavanee W, Neve RL, Orkin SH, Bruns GAP. Homozygous deletions in Wilms' tumours of a zinc-finger gene identified by chromosome jumping. *Nature* 1990; 343: 774-8.
5. Ton CC, Hirvonen H, Miwa H, *et al.* Positional cloning and characterization of a paired box- and homeobox containing gene from the aniridia region. *Cell* 1991; 67: 1059-1074.
6. Pritchard-Jones K. Controversies and advances in the management of Wilms' tumour. *Arch Dis Child* 2002; 87: 241-4.
7. Traboulsi EI, Zhu D, Maumenee IH. Aniridia. In: *Genetic Diseases of the Eye* (Oxford Monographs on Medical Genetics No. 36), Traboulsi EI, ed. New York: Oxford University Press, 1998; 99-114.

8. Schinzel A *Catalogue of Unbalanced Chromosome Aberrations in Man*, 2nd ed. New York: Walter de Gruyter, 2001; 485–90.
9. Andersen RS, Geertinger HW, Larsen M *et al.* Aniridia, cataract and gonadoblastoma in a mentally retarded girl with deletion of chromosome 11. *Ophthalmologica* 1978; 176: 171–7.

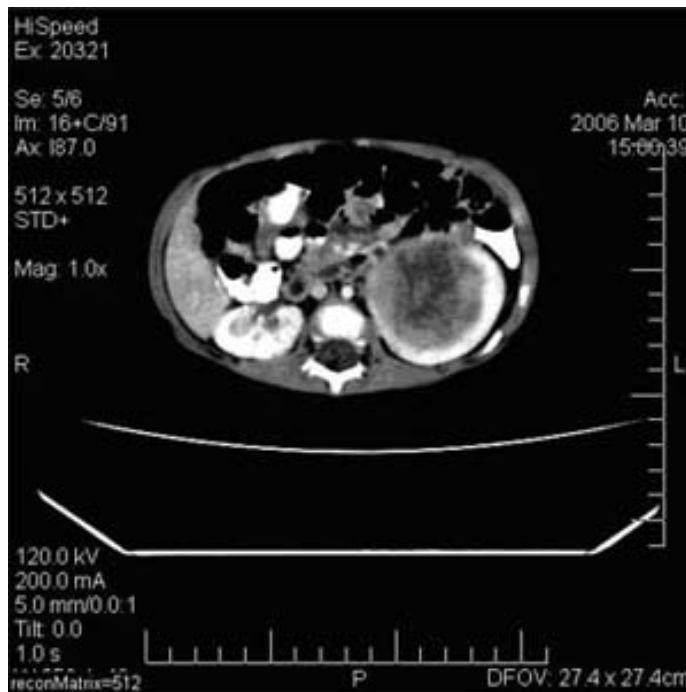


Fig.1. Wilms Tumor involving the left kidney.

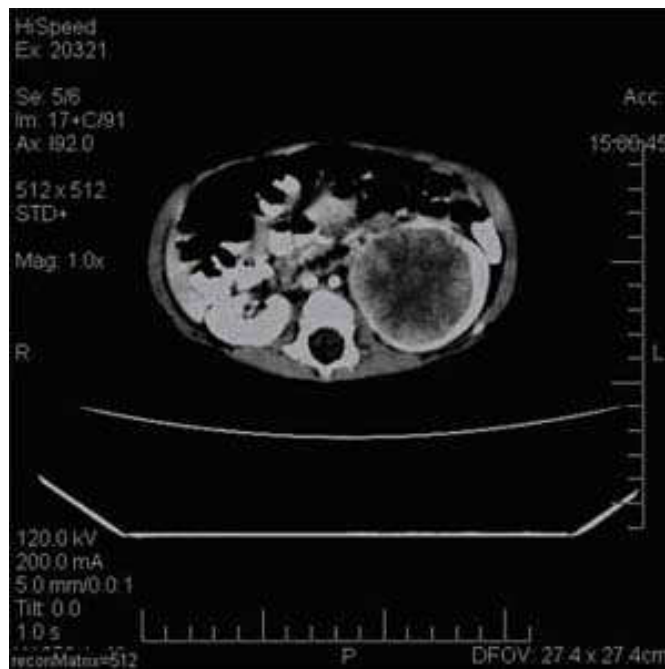


Fig .2 Wilms Tumor involving the left kidney. Small lipomatous lesion in the right intradural aspect of the spinal cord.

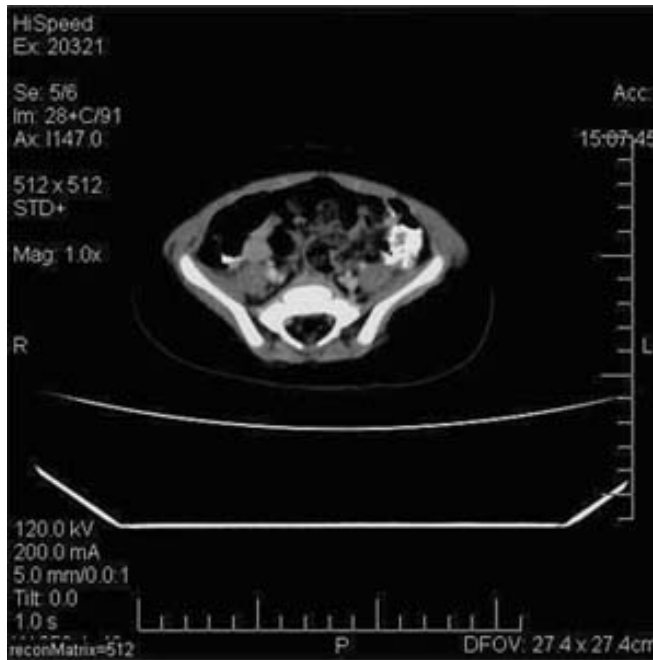


Fig. 3. Spina bifida of lower lumbar vertebrae.

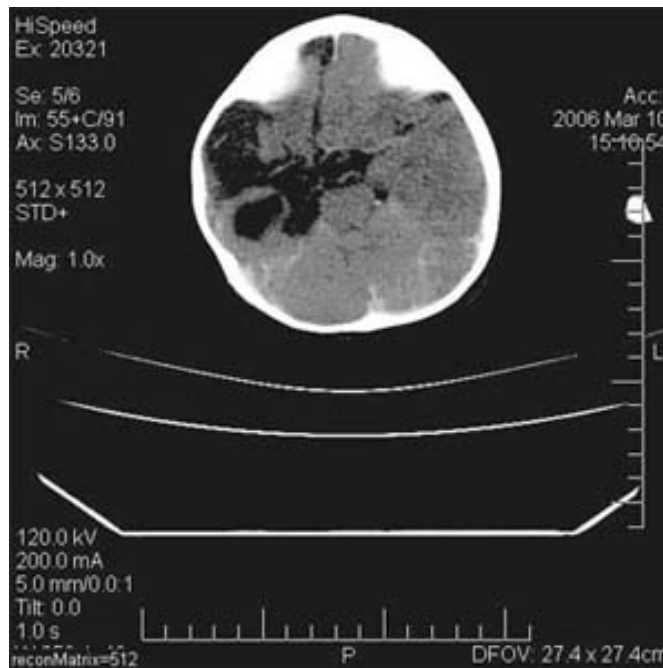


Fig. 4. Arachnoid cyst / shizencephaly in the right temporal region.

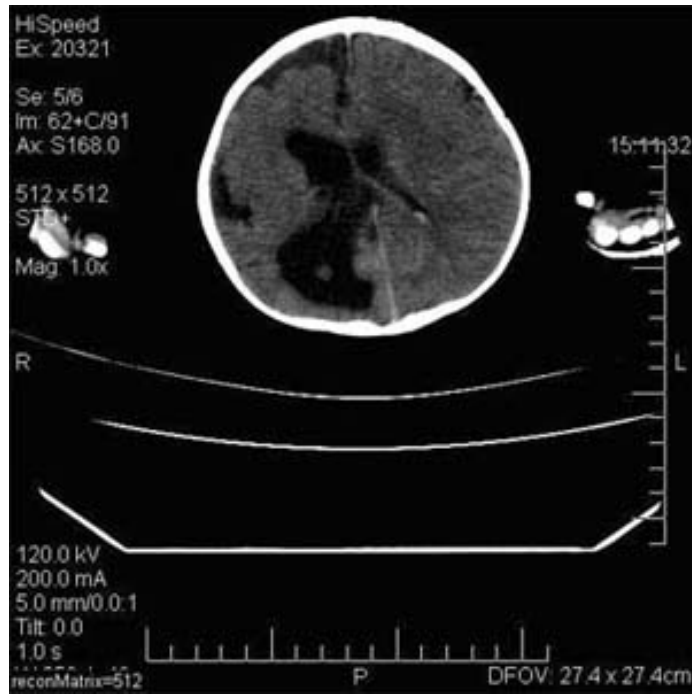


Fig. 5. Dilated right lateral ventricle with regression of right frontal lobe.

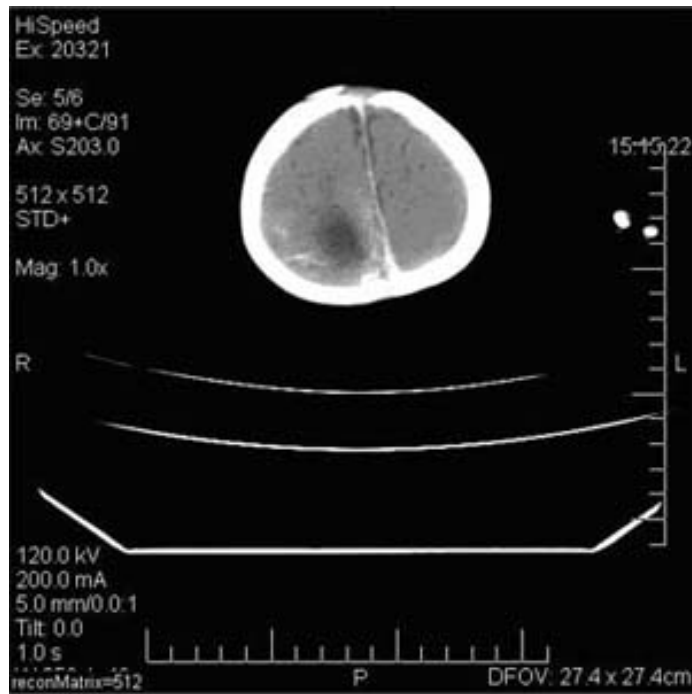


Fig. 6. Gyral enhancement in right parieto-occipital region