Wilms's tumour and aniridia: clinical and cytogenetic features

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SUMMARY A survey carried out to detect children with aniridia/Wilms's tumour syndrome identified 8 living and 3 dead children. The incidence of aniridia was found to be 1 in 43 among Wilms's tumour patients in the UK. The clinical features included complete bilateral aniridia, cataracts, glaucoma, mental retardation, hyperkinesis, hypospadias, and undescended testes. A high incidence of bilateral tumours (36%), male sex, presentation at a young age, and advanced maternal age appeared to be associated with the syndrome. The 8 living children each had a deletion on the short arm of chromosome 11. In contrast, although 2 patients with sporadic aniridia without Wilms's tumour had other malformations, neither had genitourinary anomalies, and the only additional problems in patients with familial aniridia were cataracts. Among 49 children with Wilms's tumour without aniridia only one had bilateral tumours. No chromosome abnormalities were detected in patients with familial aniridia, nor were they detected in patients with Wilms's tumour without aniridia or in those with sporadic aniridia without Wilms's tumour. While many infants with the Wilms's tumour/aniridia syndrome are clinically diagnosable at birth, chromosome analysis using the elongated chromosome method is especially valuable to confirm the diagnosis in girls with sporadic aniridia and in boys who lack the genitourinary malformations. The presence of an 11p13 deletion confirms the diagnosis of the Wilms's tumour/aniridia syndrome and indicates a very high risk for the development of Wilms's tumour.

The Wilms's tumour/aniridia syndrome was first described by Miller *et al.*¹ who reported the association of mental retardation, microcephaly, bilateral aniridia, anomalies of the pinna, Wilms's tumour, and ambiguous genitalia in males. The syndrome is generally sporadic² although familial occurrence has twice been described.^{3 4} Miller *et al.*¹ reported 6 aniridia cases in 440 patients with Wilms's tumour (1 in 73) compared with 1 in 50 000 births in the general population, and Pendergrass⁵ found 6 aniridia cases in 547 patients with Wilms's tumour (1 in 91).

Leck *et al.*⁶ found 2 cases of aniridia in 190 236 births surveyed in Birmingham (1 in 95 000). Two-thirds of aniridia cases are attributed to an autosomal dominant gene while the remaining cases are sporadic and thought to be due to a new mutation.⁷

In 1978 Riccardi *et al.*⁸ first described an interstitial deletion of the short arm of chromosome 11 in children with aniridia and Wilms's tumour. In this paper we report the incidence of the Wilms's tumour/aniridia syndrome among British patients and describe the clinical features and cytogenetic

findings. Other patients with either Wilms's tumour or aniridia were also studied and the results compared with those of the Wilms's tumour/aniridia syndrome group.

Methods

Incidence. A survey was made of children with Wilms's tumour notified to the Medical Research Council's Working Party on Embryonal Tumours between 1969 and 1978. In addition the records of all 51 children treated for Wilms's tumour at Birmingham Children's Hospital between 1969 and 1978 were reviewed. Attempts were made through the records of the Childhood Cancer Research Group and paediatric colleagues to identify other children who had presented in the UK during the same years with Wilms's tumour or aniridia. Other children with sporadic and familial aniridia, with or without additional malformations but without Wilms's tumour, were identified through ophthalmological and paediatric colleagues.

Clinical studies performed. Information was

obtained, and if possible confirmed, by interview and clinical examination (R S S). The data collected included mother's age at the birth of the child, details of congenital malformations, and family history.

Cytogenetic studies. Peripheral blood lymphocytes were set up using a standard whole blood technique stimulated with phytohaemagglutinin. Patients studied included the 8 living children with Wilms's tumour/aniridia syndrome and 10 of their parents, 3 children with sporadic aniridia, 2 mothers and 2 daughters with familial aniridia, and 6 children with unilateral Wilms's tumour who had no other congenital malformations. To achieve the high degree of resolution required to detect small interstitial deletions, every effort was made to produce elongated chromosome preparations. This was achieved by harvesting cultures after 46 hours and using a short (10 minutes) 0.002% colchicine treatment. This was found to give a reasonable yield of elongated prometaphase cells. Some cultures were also prepared using the technique of Yunis *et al.*⁹ which involves methotrexate synchronisation and precise timing of the harvesting of cells. Chromosome preparations were G-banded using the technique of Gallimore and Richardson.¹⁰

Other laboratory studies. As the deletion previously described in Wilms's tumour/aniridia patients was of the short arm of chromosome 11, attempts were made to identify other gene loci on this arm. Lactic dehydrogenase A (LDH A) is located at 11p12.03-12.08^{11 12} and therefore LDH A was studied in 4 of our Wilms's tumour/aniridia patients and in at least one parent of each. The enzyme was examined by starch gel electrophoresis. Quantitative assays of total LDH levels are unlikely to be informative in blood if LDH B is the predominant enzyme.

The gene loci for β , γ , and δ globin chains of haemoglobin are also believed to be situated on the short arm of chromosome 11, so the haemoglobin F and A2 levels were measured using the methods of Betke *et al.*¹³ and Weatherall and Clegg,¹⁴ and haemoglobin analysis was made by starch gel electrophoresis.

Results

Clinical studies. Eight children with sporadic aniridia were identified from the records of 348 children with Wilms's tumour notified to the Medical Research Council's Working Party on Embryonal Tumours, giving an incidence of 1 in 43. These records included the 51 children treated for Wilms's tumour at Birmingham Children's Hospital during the same years of whom 2 had sporadic aniridia

(1 in 25). From the records of the Childhood Cancer Research Group a further 3 children were identified with Wilms's tumour and aniridia but for only one was further information available. Two further patients were located by personal referral. Thus we present information on a total of 11 children with Wilms's tumour/aniridia syndrome. Five children and 2 adults with sporadic or familial aniridia were studied too, and clinical details are shown in Table 1. Cases 3 and 8^{4 15} have been reported previously.

The mean age of the mothers of the 11 Wilms's tumour/aniridia children at the time of birth of these children was 30.5 (range 25-41) years. This was significantly older ($P = 0.02$) than the maternal age of other children with Wilms's tumour treated at Birmingham Children's Hospital (44 cases, mean maternal age 26.4 (range 17-36) years (data not available for 5 other mothers because of adoption or emigration).

Excluding the 2 Wilms's tumour/aniridia patients, malformations were present in 7 (14%) of 49 Birmingham Children's Hospital Wilms's tumour children as follows: hemihypertrophy (2), hemihypertrophy and multiple pigmented naevi (1), Wiedemann-Beckwith syndrome (1), horseshoe kidney (1), neurofibromatosis (1), and spina bifida with hydrocephalus (1). Their clinical stages were stage I 26, II 9, III 5, IV 8, and V one (bilateral). In none was there a family history of Wilms's tumour or aniridia although the father of the child with Wiedemann-Beckwith syndrome had had macroglossia and a retroperitoneal neurilemmoma. This incidence of malformations is similar to that reported elsewhere.^{1 5} Twenty-seven of these children were boys and 22 girls.

The mean age at diagnosis of the Wilms's tumour(s) in the 11 Wilms's tumour/aniridia patients was 2.8 (range 0.6-5) years and the mean age at diagnosis of the 49 other Wilms's tumour children treated in Birmingham Children's Hospital was 4.4 years (range 2 days-8.5 years).

Cytogenetic studies. The cytogenetic findings are summarised in Table 1. No abnormalities were detected in the sporadic and familial aniridia subjects who did not have Wilms's tumour, nor were they detected in the Wilms's tumour patients without aniridia. However all 8 Wilms's tumour/aniridia children had a deletion of the short arm of chromosome 11 (Figure). The extent of the deletion varied from patient to patient, but in 6 of these the G-negative band 11p13 was missing, while in case 7 it was much reduced in size. The rest of the karyotype was normal and no translocation of the deleted material was detected. For 4 of the Wilms's tumour/aniridia patients both parents were examined and

Table 1 Clinical features of aniridia/Wilms's tumour patients and their cytogenetic findings

Case	Sex	Age at diagnosis of tumour (months)		Stage of tumour	Bilateral aniridia	Cataracts or glaucoma	Mental retardation	Undescended testes	Hypospadias	Other anomalies	Outcome	Cytogenetic findings
		1st	2nd									
Wilms's tumour/aniridia												
1	M	43	—	I	+	+	+	+	+	—	Alive	11p interstitial deletion
2	M	17	17	V	+	+	+	+	+	—	Alive	11p interstitial deletion
3	M	32	—	II	+	+	+	+	+	Diaphyseal aclasia and transient hypogammaglobulinaemia	Alive	11p interstitial deletion
4	F	12	12	V	+	—	+	—	—	—	Alive	11p interstitial deletion
5	M	60	—	I	+	+	+	+	—	—	Alive	11p interstitial deletion
6	M	7	—	II	+	+	+	—	+	—	Alive	11p interstitial deletion
7	M	9	20	V	+	+	—	+	—	—	Alive	11p interstitial deletion
8	M	11	—	III	+	+	?	—	+	—	Alive	11p interstitial deletion
9	F	43	43	V	+	+	+	+	+	—	Dead	11p interstitial deletion
10	F	32	—	I	+	+	+	—	—	—	Dead	11p interstitial deletion
11	M	48	—	IV	+	?	+	?	+	Hemihypertrophy	Dead	11p interstitial deletion
Sporadic aniridia												
Age studied (years)												
12	M	1	—	—	+	+	—	—	—	Hemihypertrophy	Alive	Normal
13	M	5	—	—	+	+	+	—	—	Congenital heart disease	Alive	Normal
14	M	4	—	—	+	—	—	—	—	—	Alive	Normal
Familial aniridia												
15	F	17	—	—	+	+	—	—	—	—	Alive	Normal
16	F	49	—	—	+	+	—	—	—	—	Alive	Normal
17	F	9	—	—	+	+	—	—	—	—	Alive	Normal
18	F	36	—	—	+	+	—	—	—	—	Alive	Normal
Present, —absent.												

+ Present, — absent.

Case 1, deletion 11p12-08-11p14-02. Case 2, deletion 11p12-08-11p14-02. Case 3, deletion 11p12-08-11p14-02. Case 4, deletion 11p12-08-11p14-02. Case 5, deletion 11p12-02-11p14-02. Case 6, deletion 11p12-08-11p14-09. Case 7, deletion 11p13-01-11p13-09. Case 8, deletion 11p12-08-11p14-02.

Figure Pairs of chromosome 11 from the 8 patients studied. In each the deleted chromosome is on the right.

found to have normal chromosomes indicating that the deletions in their children were new mutations. For 2 other Wilms's tumour/aniridia patients only the mothers could be examined and their results were normal.

Total LDH levels were normal in all of the Wilms's tumour/aniridia children and parents tested. No obvious LDH gene dosage effect was detected by electrophoresis in 3 patients but Case 5 had a shift in the LDH A pattern compatible with a single dose of LDH A. Normal haemoglobin F and A2 levels and haemoglobin electrophoresis results were obtained in those patients studied.

Discussion

These studies further illustrate the clinical features of the Wilms's tumour/aniridia syndrome and confirm the presence of interstitial deletions on the short arm of chromosome 11. As in previous reports our patients have all shown complete bilateral aniridia and a high incidence of cataracts. Mental retardation, often with hyperkinesia, was nearly always present. Undescended testes and hypospadias were present in all but one of the boys, and one child had diaphyseal aclasia and transient hypogammaglobulinaemia of infancy.¹⁵ Anomalies of the pinna and microcephaly not seen in our patients can also occur. In contrast, of the 3 children with sporadic aniridia without Wilms's tumour, although one had hemihypertrophy and another had cataracts, mental retardation, and congenital heart disease, none showed genitourinary malformations. Hemihypertrophy with or without aniridia is well known to be associated with Wilms's tumour,¹ but no tumour has yet developed in Case 12 who is now aged 3.4 years.

The only additional problem in the familial aniridia patients was cataract.

Interesting features of the Wilms's tumour/aniridia syndrome in our series include a tendency to older maternal age at birth of the affected child and a preponderance of males (8 out of 11, that is male:female ratio 2.7:1). In contrast, the ratio of males:females in the Birmingham Children's Hospital Wilms's tumour series (excluding the aniridia cases) was 1.2, and was reported to be between 0.9 and 1.8 in other Wilms's tumour populations.¹⁶ A male preponderance in the Wilms's tumour/aniridia syndrome has been noted previously.¹⁷

As in other series^{1 2 5 18} the tumours tended to present at a younger age in our patients with aniridia than in the general population of Wilms's tumour cases, but there was a wide range (7-60 months). The extremely high incidence of bilateral tumours (36%) in our Wilms's tumour/aniridia patients contrasts strikingly with an incidence of 2% in the other Birmingham Children's Hospital Wilms's tumour cases and of 4.4% in a large general Wilms's tumour population.¹⁹ In a series of 11 children reported by Bond²⁰ bilaterality was associated with older maternal age, a high incidence of malformations (including aniridia in one child), and young age at presentation of the tumours.

The overall incidence of aniridia in our British Wilms's tumour patients (1 in 43) appears higher than in the American series^{1 5} but may not differ significantly from the pooled estimate of their two and our series of 1 in 67.

All children with the Wilms's tumour/aniridia syndrome studied to date by the elongated chromosome method have had 11p13 deletions (Table 2). Thus, while many infants with the syndrome are clinically recognisable at birth, chromosome studies will be helpful in some babies with aniridia to identify those likely to develop Wilms's tumour, particularly girls, who do not show the genitourinary malformations, and cases of sporadic aniridia without other apparent defects. Our Case 7

Table 2 Reported cases of chromosomal abnormalities in aniridia/Wilms's tumour syndrome*

Case	Sex	Age at diagnosis (months)	Bilateral disease	Mentally retarded	Genitourinary anomalies
18	M	42	None	Yes	Present
223-26	F	36	None	Yes	None
311	M	19	None	Yes	None
43	M	15	Present	Yes	Present
527	M	10	None	Yes	Present
627	F	12	None	Yes	None
7-10 ²⁸		Not recorded			
11-14 ²⁹		Not recorded			

*Excluding cases 1-622 described in this paper.

was of special interest because his only malformations were bilateral aniridia and cataracts, yet he developed bilateral Wilms's tumours. It is probably relevant that in him the deletion was shorter than that present in any other Wilms's tumour/aniridia case we studied. At birth it would have been difficult clinically to determine that his risk of Wilms's tumour was greater than that for the other children (Cases 12-14) with sporadic aniridia. Thus chromosome analysis should prove to be particularly valuable in babies with sporadic aniridia who lack the other feature of the Wilms's tumour/aniridia syndrome, to predict those at risk of Wilms's tumour.

Although we confirmed the presence of interstitial deletions of the short arm of chromosome 11 in children with Wilms's tumour and aniridia, unlike Riccardi *et al.*⁸ we could not demonstrate this deletion in patients with aniridia alone, whether sporadic or familial, nor could we find it in those with Wilms's tumour alone. A deletion in the 11p13 region has also been reported in a girl with aniridia, cataracts, mental retardation, and gonadoblastoma.²¹

Familial occurrence of the Wilms's tumour/aniridia syndrome has been described in a family in whom the proband showed a deletion of most of band 11p13 and of sub-band 11p14.1 and in whom the proband's mother and brother, who were both phenotypically normal, showed a balanced chromosomal rearrangement.³ Thus it seems clear that the 11p13 region contains a gene necessary for proper development of the iris and urogenital system and a locus which when absent predisposes to the development of malignancy, especially Wilms's tumour. However, since many cases of aniridia alone do not have deletion of 11p13, a deletion is not the only reason for this condition, which could be caused by point mutations at the same locus or by defects at other loci controlling development of the iris.

Although our studies are inconclusive, they may indicate that the locus for LDH is also situated in the 11p13 region, whereas the loci for the globin genes are not.

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