

Wilm's-aniridia syndrome with transient hypo- γ -globulinaemia of infancy

Aniridia is the only congenital malformation linked in significant numbers with the subsequent development of Wilm's tumour (Miller, Fraumeni, and Manning, 1964). Though aniridia is usually inherited as an autosomal dominant, with 2 of 3 affected children having 1 affected parent, children with the Wilm's-aniridia syndrome only very rarely have a parent with aniridia (Miller, 1968; Fraumeni and Glass, 1968). The syndrome is characterized by aniridia, secondary cataracts, microcephaly with mental retardation, a folding-over of the pinna, and anomalies of the urinary tract with Wilm's tumour. We report a case of Wilm's-aniridia syndrome where development of the tumour was preceded by development and recovery from transient hypo- γ -globulinaemia of infancy.

Case report

The patient was the second child of normal parents. There was no parental consanguinity. He weighed 3.7 kg at birth and 9.3 kg at the age of 1 year. The mother's brother had had a bad chest until the age of 7 years, but there was no family history of eye trouble, tendency to infection, or malignant disease.

At birth he would not open his eyes, and later the mother noticed that the eyes had no colour. Bilateral aniridia was diagnosed at the age of 9 weeks and at the same time two large lacunae of the left occipitoparietal region and a large anterior fontanelle were noted. The top of the pinnae were folded over. Later he developed bilateral buphthalmos, glaucoma, and lens opacities.

At 9 weeks he developed croup. Subsequently he required repeated anaesthetics for the management of the eye condition, and several of these were complicated by postoperative chest symptoms with an asthmatic element. For this reason it was necessary to postpone the operation on several occasions. Investigations showed deficiency of serum IgG (Table).

At 5 months of age he had eczema of the face and neck, and a napkin rash. On a milk-free diet the skin manifestations cleared and there was no recurrence of the wheeziness for several months. He was subsequently troubled by recurrent coughs and colds and was treated with antibiotics. At the age of 14 months it was thought that a single injection of γ -globulin (10 ml)

TABLE
Serum immunoglobulin levels (mg/100 ml)

	IgG	IgA	IgM	Age (mth)
Patient	100	14	36	4
	<100	12	64	5
	900	33	68	12
	640	45	135	13
	1025	45	96	14
	1450	130	165	26
	703	57	76	32
	824	109	60	4½ yr
Mother	1006	145	202	—

before anaesthesia reduced the tendency to postoperative chest infection, though by now serum immunoglobulin levels were normal.

At the age of 32 months he developed haematuria. The kidneys were not palpable, but intravenous pyelography showed a large tumour in the upper pole of the right kidney which proved to be a nephroblastoma. It was removed at operation. The left kidney was normal. Actinomycin D 195 mg was given at the time of operation and subsequently for 4 days. A week later he was given radiotherapy, a total dose of 2500 rads to the whole abdomen, with shielding of the remaining kidney at 2000 rads. He subsequently received courses of vincristine. At the age of 4½ years he is alive, but mentally retarded. He can say only a few words, and little of his speech is recognizable. Merrill-Palmer test showed a mental age of 2 years 1 month, and he passed 4 items on the Stanford-Binet scale at the 2-year level. Assessment was rendered difficult by the combination of visual and speech defects.

Investigations. Serum immunoglobulins were measured by radial immunodiffusion using Hyland Immunoplates. The initial immunoglobulin estimation at the age of 3 months showed a low IgG of 100 mg/100 ml with low normal IgA and normal IgM. 2 months later the IgG had fallen to below 100 mg/100 ml, IgA was unchanged, and IgM had risen. There was a subsequent rise of immunoglobulins to normal levels (Table). His mother's immunoglobulin levels were normal.

His blood group was O Rh (D) positive. At the age of 13 months the isoagglutinins were anti-A 1/64, anti-B 1/8. Peripheral blood counts showed normal white cells (7900 to 9500/ μ l) with normal differential counts. Absolute lymphocyte counts ranged from 3330 to 5310/ μ l, with normal small lymphocytes.

Delayed hypersensitivity to dinitrochlorobenzene (DNCEB) was induced at the age of 13 months by applying 2 mg in acetone to a 1 cm² area of the forearm. No delayed reaction followed, and no reaction was provoked by the application of a further dose of 0.02 mg 2 weeks later; but a third dose of 0.04 mg at the age of 14 months produced a normal delayed hypersensitivity reaction, with a wheal and vesicles. He was still positive at the age of 4½ years with a 0.05 mg dose, when a weak delayed reaction to candida 0.1% was also shown.

Antibody was not detected to herpes simplex, cytomegalovirus, or rubella at the age of 14 months. One month after measles inoculation the titre of measles antibody was 1/64, at 26 months of age.

Comment

This boy clearly has the Wilm's-aniridia syndrome together with a temporary state of delayed development of immunoglobulins. A clinical picture of eczema, allergy, and tendency to recurrent infection associated with low IgG, low normal IgA, and normal IgM in the early months of life, which spontaneously improves, is characteristic of a relatively common disorder of the immune response, transient hypo- γ -globulinaemia of infancy. In our experience children with this disorder may develop eczema, vomiting, diarrhoea, and failure to thrive which recover spontaneously as the child's immunoglobulins rise to normal. We are not aware of any other children with the syndrome who have developed malignant disease. Frommel and Good (1971) postulate that the syndrome is due to relative inability to produce a normal primary response of macroglobulin type (21S) and consequent failure to convert to 7S (IgG and IgA) antibody production. The syndrome may be familial.

In 1968, Fraumeni and Glass summarized 22 cases of Wilm's tumour associated with aniridia, and since then further reports of at least 5 other cases have appeared (Surugue, 1967; Mackintosh *et al.*, 1968; Woodard and Levine, 1969; Haicken and Miller, 1971). Another case has been personally reported to us in Manchester by Dr. P. M. Jones. This brings the total number of recorded cases to at least 29. No mention of immunoglobulin levels or predisposition to allergy or infection have been recorded, but this does not exclude the possibility that other cases may have had low levels of IgG at some time before the diagnosis of Wilm's tumour.

We suggest that serum immunoglobulins be monitored in the early months of life in future cases of congenital aniridia. Other cases may be found; and further cases of transient hypo- γ -globulinaemia with the Wilm's-aniridia syndrome would be most interesting, both from the general point of view, as illustrating further the relation between immune

deficiency and malignancy, and as an indicator, perhaps specific, of the premalignant state in the individual case.

Summary

A case of Wilm's-aniridia syndrome is presented. Initial management of aniridia was complicated by infection and asthma, and low IgG was discovered. Immunological status subsequently developed normally, with normal immunoglobulins, normal antibody levels, and normal delayed hypersensitivity tests. Wilm's tumour was diagnosed at 32 months. Immunological studies should be made in other cases of congenital aniridia.

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Immunoglobulins in normal infant born of severe hypo- γ -globulinaemic mother

Immunological maturation in normal infants born of normal mothers is well known (Berg, 1969). But there are few reports dealing with infants of mothers with immunoglobulin deficiencies. Bridges *et al.* (1959) and Zak and Good (1959) have reported a rise