Wilm's Tumor and Congenital Malformations

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Wilm's tumor is thought to be hereditary, and histological studies have indicated that it may be an embryonic defect. Most frequently this tumor forms in the neo-natal period or in early childhood, but it has also sometimes been seen in the fetus. Wilm's tumor is associated with other congenital malformations, which are most frequently aniridia, genito-urinary defects, and hamartomatous lesions; hemihypertrophy is also not uncommonly seen. Lenstrup was the first to report hemihypertropy and surrenal hyperplasia in 1927,[1] and other reports followed.[2-9] We present a case of Wilm's tumor seen in November 1968 which was referred to us for operation by another hospital. Noticing that the patient had hemihypertrophia, we did research on 76 other cases of Wilm's tumor seen here between January 1958 and September 1968. The aim of this paper is to bring to the attention of pediatricians the fact that since hemihypertrophia is often associated with Wilm's tumor, hemihypertrophic children should always be checked for the latter condition.

Case Report: G.A. 68/65219, a seven-month-old female, born after a normal pregnancy, the birthweight was unknown. She had had nystagmus since birth, and 15 days before the parents brought the child to the hospital they noticed that the left abdomen was swollen.

Family History: The patient was the first child of unrelated parents, a previous pregnancy having ended in miscarriage at three months. The mother was 25 and the father 32 years old.

Physical Examination: Weight 9.100 gr (<97 per cent), length 73 cm (<97 per cent), head, chest and abdomen circumferences were 45, 46 and 51 cms respectively. The skull was asymmetric, and the right side of the face was more prominent than the left. The right ear was turned over laterally and anteriorly, and the eyes were slightly enopthalmic with

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lateral strabismus and nystagmus. The left leg was bigger than right. The upper alveola and tongue were wider than normal.

Laboratory Findings: Hb. 7.5 gr/100 ml, WBC 10,000/mm^3, NPN: 33 mg/100 ml. Skull x-ray showed the left side of the chin to be more hypoplastic than the right (Figure 1). Abdominal x-ray showed a mass on the right side, (Figure 2) and intravenous pyelogram revealed a mass in the upper part of the right kidney.

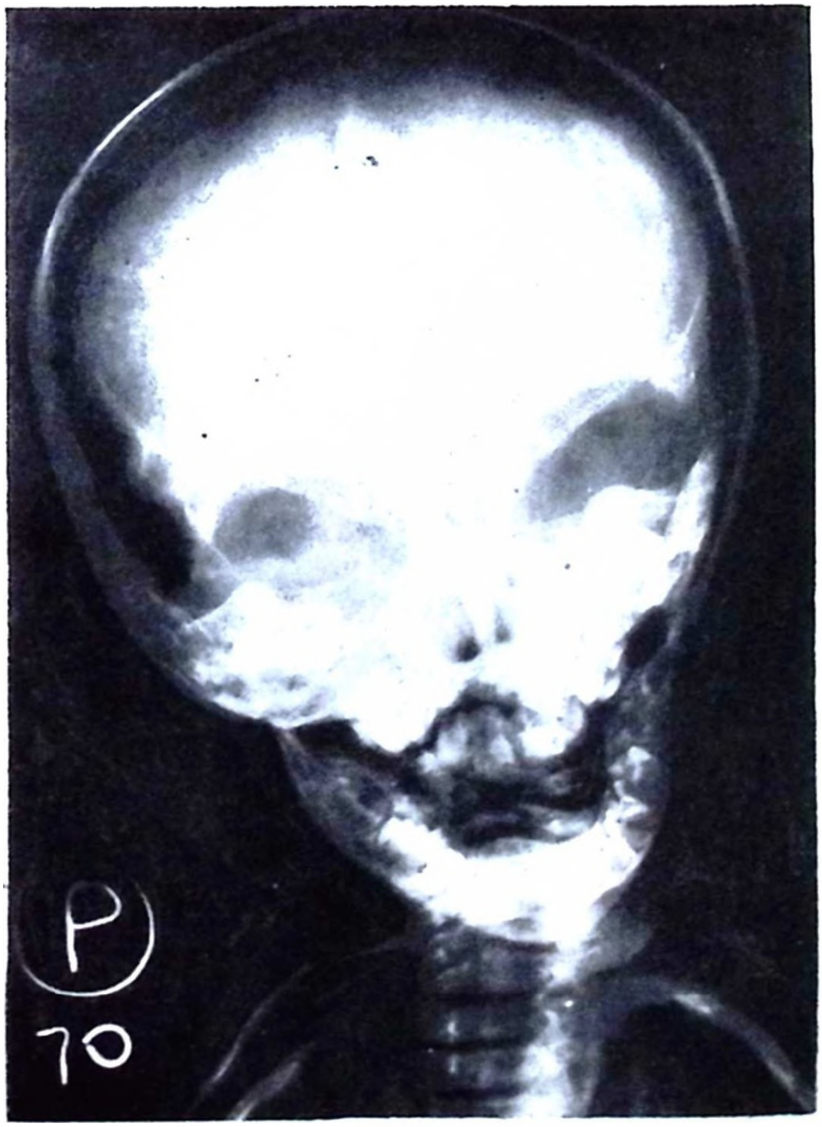

Figure 1

The patient was operated on 22/11/1968. Left nephrectomy was performed and the tumor was removed. For the first five post-operative days 100 mg actinomycin D and radiation treatment. were given. On the sixth day the blood count was found to be 4,400/mm^3 and on the seventh 2,600/mm^3, at which time radiation was discontinued. In the

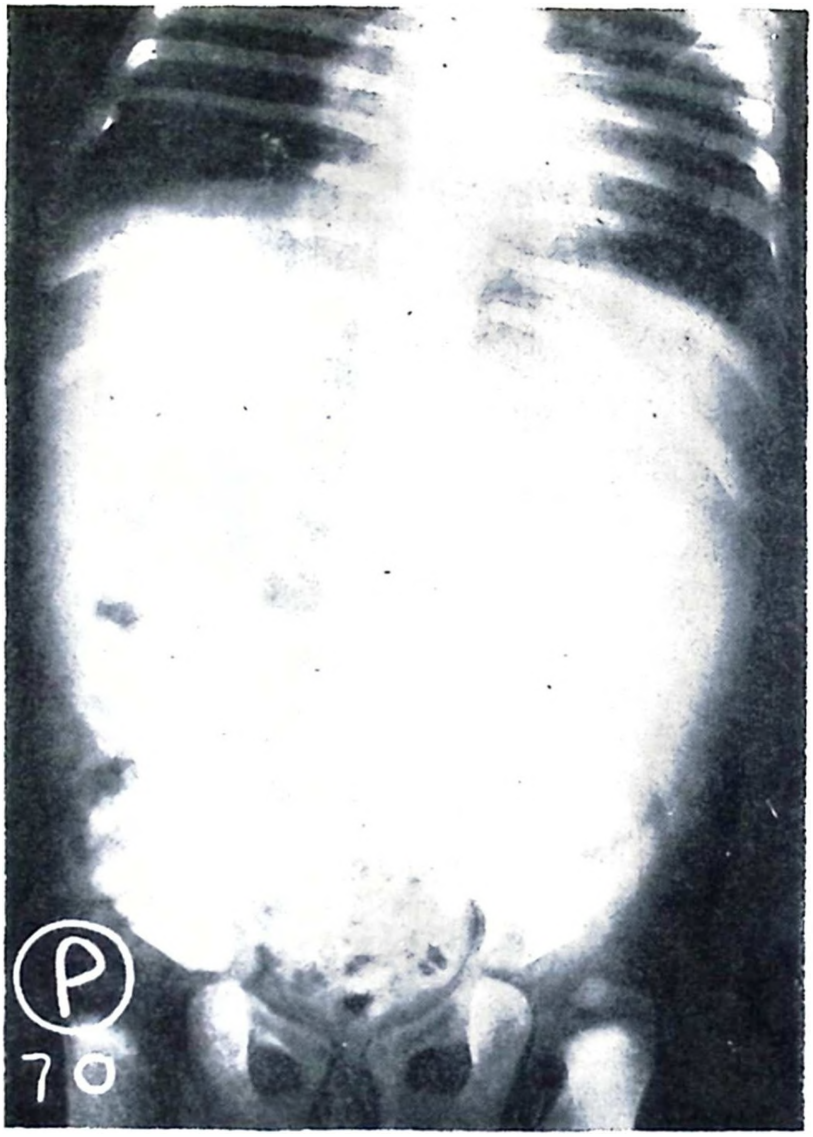

Figure 2

first post operative days the temperature rose to 39.3° C, and the patients was given chloromphenicol and penicillin treatment. The leukocyte count decreased to 1,200 and the patient was given a fresh blood transfusion. Her condition continued to deteriorate, so tracheotomy was performed, but without success, and the patient expired. Histological pathology revealed Wilm's tumor.

Dermatoglyphic Findings : The dermatoglyphic findings of this patient and others with hemiphypertrophy and Wilm's tumor are shown in (Picture 3-4) Our patient showed very similar, symmetrical palms, which appears to contradict the hemiphypertrophic condition. The other findings were axial triradius which was not in the normal t' position but in a t'' position, and the atd angle was more than 56°. The basic A line

was longitudinal, which is rare in this condition, and the fingers showed raised arches (Figure 3). The dermatoglyphic findings of Case 9 in Table 1 are shown in Figure 4.

Seventy-six charts of patients with Wilm's tumor seen in this hospital between January 1958 and September 1969 were reviewed. We were helped in the diagnosis of congenital abnormalities by x-rays, post mortem studies, biopsies and operation reports. These are summarized in Table I.

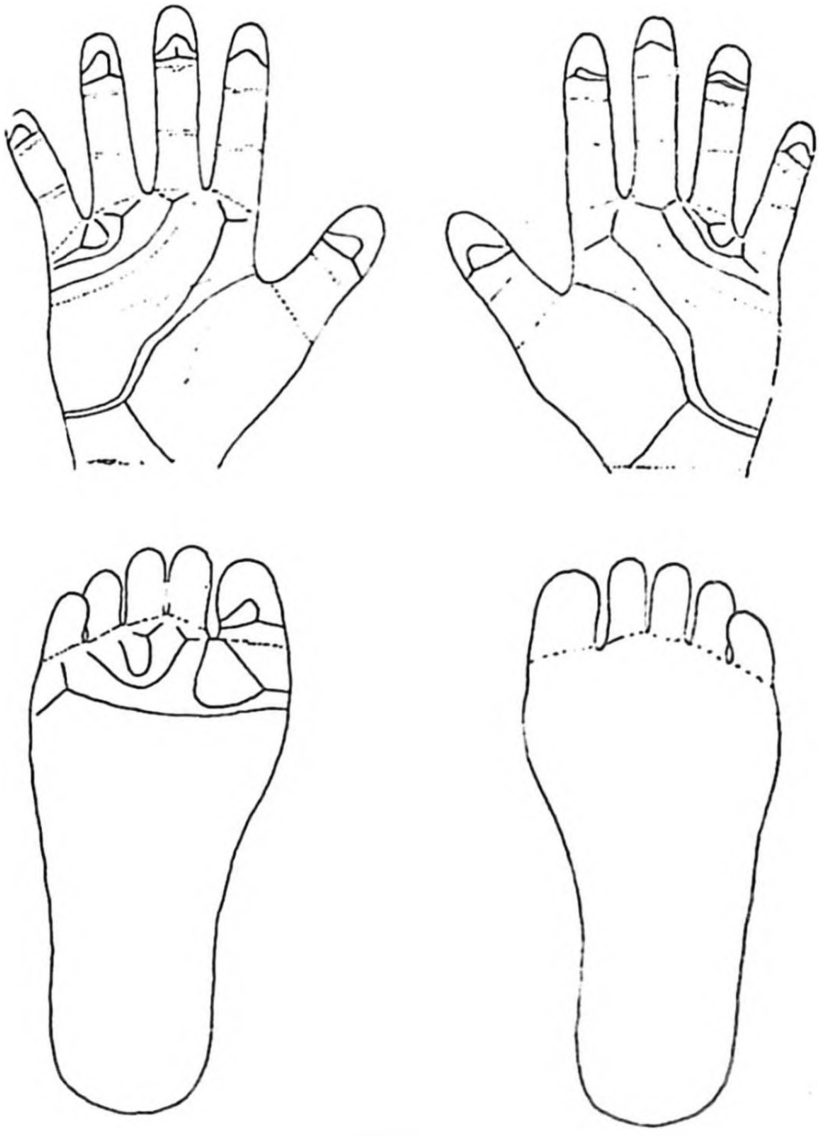

Figure 3

Discussion

Until 1967, 26 cases of congenital hemihypertrophy associated with Wilm's tumor had been reported in the literature.[8] As it is well

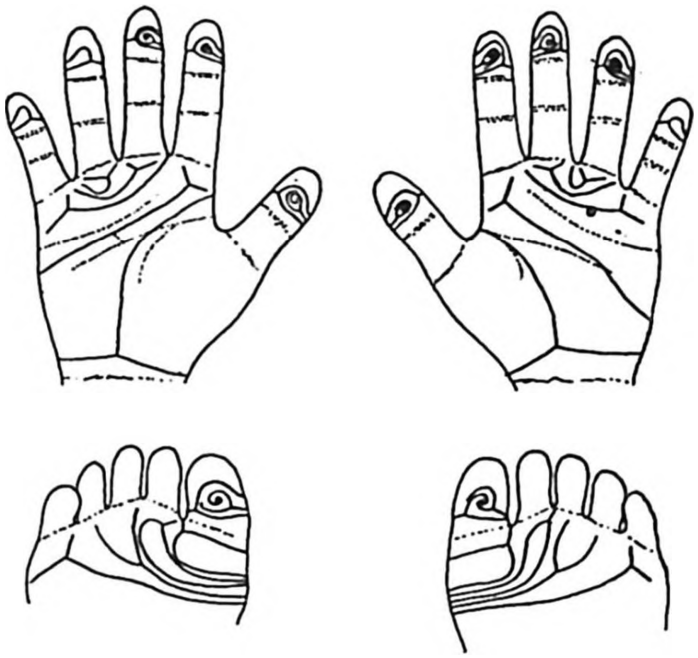

Figure 4

known, this tumor is related to other congenital anomalies, of which aniridia, hypospadias, cryptorchism and horseshoe kidney are the most common. It is also connected with genetic diseases. For example, Miller et al studying 440 cases found that Wilm's tumor was associated with neurofibromastosis, congenital spherocytic anemia and various chromosomal aberrations,[2] and the latest reports, showing it to be associated with 18-trisomy, are particularly interesting.[10 11] Congenital hemihypertrophy is associated with other congenital malignant tumors besides Wilm's tumor, such as adrenal neoplasm, hepatoblastoma and abdominosarcoma.[2 4 12 13] Such non-malignant tumors as hemangiomas, fibrolipoma and adenomatous polyps have also been reported with Wilm's tumor.[2]

It is still not known why the very rare entity of hemihypertrophy is associated with Wilm's tumor, but sex may play an important role. For example, our patient was female, as were 73 per cent the other cases reported.[8] No correlation has been seen between the location of the tumor and the side of hemihypertrophy, but 15 per cent of Wilm's tumors are on the same side as hemihypertrophy. However, congenital hemihypertrophy may be very diffuse, showing no correlation with the tumor,[9] as, for example, when it is limited to the face and tongue in a patient with Wilm's tumor.[8] Congenital hemihypertrophy may be related to other such entities as benign and malign tumors, but most frequently with Wilms' tumor, and it is therefore important in understanding the etiology of the tumor.

In many cases of Wilms tumor genetic findings have played an important part, and eight families with more than one child (and one with four children) have been reported with this disease. However, this is not always the case, and often other members of the family are unaffected. [7 14 15]

The role of inheritance is still unknown in congenital hemihypertrophy. Three families have been reported with the condition, one where the mother and her daughters were affected,[16-17] in another the mother and sons were affected [18] and four cases where one other member of the family was affected.[19] If the relationship between inheritance and this disease is to be understood, patients who have been cured of Wilms' tumor should be followed up for many years.

The association between Wilm's tumor and congenital hemi hypertrophy may be a newly discovered link between congenital malformations and malignancy. These two pathologies are frequently related to mental retardation, syndactyly, multiple pigmented nevi, hemangioma, cryptorchism, hypospadias, hypogonadism and other genito-urinary system disturbances.[2 5 8] Horseshoe kidney, aplastic or hypoplastic kidney and urethral anomalies are also more often seen in patients with Wilms' tumor than in the normal population. Such defects may be seen more frequently with congenital hemihypertrophy, too, and sometimes this pathology resembles that found with Wilms' tumor. Another important point is that polycystic kidney is also associated with Wilms' tumor.[20]

Congenital hemihypertrophy and Wilms' tumor may coincide with other adrenal tumors and liver malignancy. In the normal population the two sides of the body are never identical in size, and normal people may have difference between two halves of the body which are not noticeable. But in the reported cases of hemiphypertrophy with Wilms' tumor the difference between the two is very marked. If the correlation between Wilms' tumor and hemihypertrophy is to be understood the exact incidence of the latter condition in the normal population should be established, but as yet we have no knowledge of this subject. Fraumeni et al reported 225 cases of Wilms' tumor of which seven also had congenital hemihypertrophy; which seems to be more than a coincidence.[8]

Congenital aniridia also has an interesting relation to Wilms' tumor. A study was made of patients with the latter, and the ratio was found to be 1/73. Shaw, Falls and Neel found aniridia in 1/50,000 newborns, which shows that the correlation between this and Wilms' tumor is high. These authors also showed in their studies that aniridia in man is caused

by the action of an almost completely penetrant dominant autosomal gene which has almost no phenocopies.

Many cases of Wilms' tumor reported in the literature have shown chromosomal anomalies. Among these an extra E group chromosome is seen, and both 16 chromosomes have extended long arms.[8] Eighteen mosaic trisomy have been seen,[10-11] and in two cases skin culture showed diploid-triploid mosacisim but not in leukocytes.[23-24] In another case 45-46 mosaicism was seen in the skin and the leukocytes,[25] while another had one No.3 chromosome larger than the other.[26] Another case showed triploidy on the hypertrophic side,[27] but since this finding may have been due to a technical error, such a relationship is subject to doubt. In other patients with hemihypertophy associated with Wilms' tumor, chromosome analyses have been structurally and numerically normal, and in those with chromosome abnormalities there is usually mental and growth retardation. It is possible, therefore, that the cases with chromosome anomalies may be a separate entity or that they may result from hemiatrophy rather than hemiphypertrophy. (Table II shows Case 2, which was interesting from this point of view. The chromosome constitution resembled that seen in Turner's syndrome, with anal atresia. A separate report will be written on this patient.)

It may be thought that hemihypertrophy and hemiatrophy could be caused by embryonic defects, or by an early zygotic division abnormality. The side of the body or one of the zygotic segments may be in chromosomal imbalance, which could explain congenital asymmetry and mosaicism. But this cannot explain all cases of congenital hemihypertrophy with mosaicism or those with large chromosomes. Why, then, do so few children born with mosaicism have hemihypertrophy as well? There does not seem to be an answer to this question.

Fraumeni et al found no dermatoglyphic abnormalities or asymmetry in four patients with Wilms' tumor and congenital hemihypertrophy; they explained than the reason for this could be that asymmetry develops later in intrauterine life.[8]

Johnson and Penrose studying nine cases of congenital hemihypertrophy found minor, unimportant bilateral differences.[28]

Dermatoglyphic analysis of our patients gave results similar to those of Fraumeni et al. There was no dermatoglyphic asymetry, but the axial triradius showed t" position in the case described which has not been reported before in the literature. There was no asymmetry in the dermal pattern of the palms.

TABLE II

CONGENITAL MALFORMATION IN 76 WILM'S TUMOR CASES

Case	Age sex (Yr)	Location of Tumor	Eye findings	Hemihypertrophy	Syndactyly	Hypospadias	Cryptorchism	Other findings
1	7 12 Female	Left	Nystagmus lat. strabismus enophthalmia	Facial asymmetry, hemihypertrophy of the left leg	–	–	–	Deformed right ear
2	10 Female	Right	Lateral strabismus, hypertelorism	–	–	–	–	Her sister died from anal atresia, grandmother and grandfather had had Ca. the patient also had microcephaly, rectovaginal fistul, anal atresia, mental retardation, multiple nevus, bladder stones, chromosomal anomalies. 45xo
3	1,5 Male	Left	–	–	Bil. 2-3 rd toes	+		–
4	21 Male	Right	–	–	–	–	+	–
5	14 12 Male	Left	–	–	–	–	–	Nevus right lumbal area.
6	1 Female	Left	–	–	Bil. 2-3 rd toes	–		–
7	3 Male	Left	–	–	–	–	–	Spina bifida L^5 – S^1
8	1 Female	Left	–	–	–	–	–	Right double urether and aberrant spleen
9	13 12 Male	Right	Slight microphthalmia of the left eye.	Right sided " sided " sided	–	–	–	–
10	14 12 Male	Left	–	–	–	–	–	Deformed ears

Summary

Cases of Wilms' tumor seen at Hacettepe Medical Center Children's Hospital between January 1958 and September 1969 are reviewed. Seventy-six patients were seen of whom ten also had various congenital malformations two of whom had hemihypertrophy, and one had Turner's syndrome. The etiopathogenesis of congenital hemiphypertrophy and its association with Wilms' tumor, are discussed.

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