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BILATERAL NEPHROBLASTOMA

A clinical review of 19 cases

by

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The prognosis in bilateral nephroblastoma remains poor although in the last two decades occasional reports of survivors have appeared (1—5, 8—10, 20, 27, 28, 31). The 19 bilateral cases now reviewed occurred among 334 cases of this condition reported in the Scandinavian countries between 1927 and 1967 — an incidence of 5.7 per cent. Thirteen were treated in Sweden, 2 in Norway and 4 cases in Finland.

Bilateral nephroblastomas present some interesting clinical features; the prognosis is poorer than for the unilateral tumour and the patients are younger. The diagnostic problems are reflected in the difficulty of choosing the appropriate therapy, and in the need for numerous compromises. Associated congenital anomalies are frequent.

Material. All the patients in whom nephroblastoma was detected in both kidneys during life have for the purpose of this review been considered as having bilateral nephroblastoma. Eleven of the 19 patients (8 girls and 11 boys) were under one year of age, one was 13 months, three were 3 years, three were 4 years

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Table 1

Two-year cure rate for three methods of treatment of 15 patients of the present series (2 received no treatment and 2 were operated upon only)

	Bilateral irradiation				Unilateral irradiation			
	No chemo-therapy		Chemotherapy		No chemo-therapy		Chemotherapy	
	No.	Cured	No.	Cured	No.	Cured	No.	Cured
Nephrectomy+resection	—	—	3	2	5	0	2	1
Unilateral nephrectomy	1	0	3	0	—	—	—	—
Unilateral resection	—	—	1	1	—	—	—	—

and one 5 years old. The first sign of the disease in 7 children was haematuria and in the remaining 12 children was an abdominal swelling. Haematuria is more common in bilateral than in unilateral nephroblastoma (13). The abdominal swelling had been observed shortly after birth in 2 children but in one of these, four months elapsed before a diagnosis was made — when the swelling started to increase — and in the other a sudden change in the appearances of 'bilateral cystic kidneys' at three years led to discovery of a tumour. Bilateral nephroblastoma was present in a 5-year-old girl who had been under medical supervision for two years for 'bilateral malformation of the kidneys'.

Bilateral disease was diagnosed before the first treatment in 13 patients, one of whom had pulmonary metastases on admission. The tumour in the second kidney was noticed later in 6 patients, in 4 of these within a year of the first treatment, in one after six and in the last after nine years. Metastases were detected, at the same time as the tumour, in the second kidney in 3 patients. Associated congenital malformations were present in 3 patients, bilateral kryptorchismus in 2 of these, one of whom also had hypospadias, while the third was a male intersex.

Two patients received no treatment at all and 2 only surgery, while in 15 patients surgery, radiotherapy and chemotherapy were combined (Table 1). Irradiation was applied to 26 tumour bed regions in 15 patients. In one patient given bilateral irradiation the dose is unknown, and in one the dose was 1 000 rad to each side. One patient was treated on three occasions for recurrence, and over a period of 2 years received a dose of 4 300 rad to each region. The dose ranged from 1 500 to 3 000 rad in 12 patients and 18 regions. Radiotherapy was given before operation in 4 patients.

Table 2

Two-year cure rate for the various methods of treatment of 19 patients

	No. of cases	Cured
No treatment	2	—
Operation only	2*	—
Unilateral operation + bilateral irradiation	5	1
Bilateral operation + unilateral irradiation	7	1
Bilateral operation + bilateral irradiation	3	2

* One patient died at operation

Results

Patients free of symptoms for at least two years were regarded as cured since in an earlier series no metastases occurred more than fifteen months after the operation. Of the 6 patients treated in the period 1943—59 none survived. Of the 13 patients treated between 1960 and 1966 4 were alive and well at least two years after the last treatment; 3 of these were less than one year old, and the fourth was thirteen months old on admission. The two-year cure rate for the various methods of treatment is given in Table 2.

Case reports

Case 1. Boy, aged 9 months, who in November 1966 underwent right nephrectomy and ureterectomy for nephroblastoma twice the size of a man's fist; the left kidney appeared to be normal. Cyclophosphamide was given on the day of the operation and on each of the next 9 days together with 2 500 rad to the tumour bed over a period of four weeks. Haematuria occurred in June 1967. Surgical exploration after inconclusive urography revealed no neoplasm. Exploration in November 1967 after another episode of haematuria disclosed a growth in the upper lobe and two tumours in the central part of the left kidney. Partial resection of the left kidney was followed by a course of cyclophosphamide. More than two years after the last treatment the patient was without signs of a neoplasm or impaired renal functions.

Case 2. Boy, aged 11 months. Exploratory laparotomy in September 1963 confirmed the clinical diagnosis of bilateral nephroblastoma with lymph-node metastases. Treatment consisted of 2 000 rad over four weeks to the left kidney and 1 000 rad over two weeks to the right kidney with actinomycin D, the latter repeated every two months. In June 1964 a recurrence in the left kidney initiated approximately 1 100 rad to the left and 2 300 rad to the right kidney. In January 1965, the residual mass was partially resected from the left kidney and actinomycin D given for six consecutive days. Another 1 000 rad was delivered to both kidneys over a period of one week. In August 1965, complete failure of the left

Table 3

Fifteen patients with bilateral nephroblastoma treated during the period 1943—1967

Sex	Age	First sign	Date of diagnosis	Stage at first treatment	Treatment	Death	
						Date	Stage
♂	10 mos	Abdominal swelling	June 1943	Left: — Right: Fixation, inoperable	None	Nov. 1943	Primary tumour, bilat. No metastases
♀	4 mos	Abdominal swelling	Nov. 1964 Dec. 1955	Left: Pulmonary metastases Right: Encapsulated	Irradiation, 1500 rad. Actinomycin D Nephrectomy + irradiation (dose unknown)	Feb. 1965	Primary tumour, left. Metastases
♀	5 yrs	Haematuria	Sept. 1958	Left: Lymph node metastases Right: Extension beyond the capsule and invasion of vessels	Nephrectomy + irradiation, 1500 rad Resection	Jan. 1959	? Primary tumour No mestastases
♂	7 mos	Abdominal swelling	Dec. 1958	Left: — Right: —	None	Jan. 1959	Primary tumour, bilat. No metastases
♂	6 mos	Abdominal swelling	Dec. 1959	Left: Encapsulated Right: Invasion of vessels	Nephrectomy + irradiation, 1500 rad Resection (not radical)	Jan. 1961	Primary tumour, right. No metastases
♀	3 yrs	Haematuria	Sept. 1959 Feb. 1959	Left: Pulmonary mestastases Right: Encapsulated	Irradiation, 2500 rad Nephrectomy + irradiation, 1500 rad	June 1960	Primary tumour, left. ? Metastases
♀	3 yrs	Haematuria	March 1959	Left: Invasion of vessels Right: Fixation, inoperable	Nephrectomy + irradiation, 2200 rad. Actinomycin D Biopsy + irradiation, 2200 rad. Actinomycin D	Dec. 1959	Primary tumour, bilat. Metastases
♂	7 mos	Abdominal swelling + haematuria	Sept. 1960	Left: Encapsulated Right: Encapsulated	Resection + irradiation, 1900 rad Nephrectomy	April 1962	Primary tumour, left. No metastases

Table 3 *(cont.)*

Sex	Age	First sign	Date of diagnosis	Stage at first treatment	Treatment	Death	
						Date	Stage
♀	3 yrs	Abdominal swelling	Sept. 1963	Left: Extension beyond the capsule Right: —	Nephrectomy None	Feb. 1964	Primary tumour, right. Metastases
♀	11 mos	Abdominal swelling	Oct. 1960	Left: Encapsulated Right: Invasion of vessels	Resection Irradiation, 1300 rad, nephrectomy + irradiation, 1000 rad	Oct. 1961	Primary tumour, left. Metastases
♀	4 yrs	Abdominal swelling	April 1962	Left: Encapsulated Right: Burst at operation	Nephrectomy + irradiation, 1500 rad Resection	March 1963	Primary tumour, bilat. Metastases
♂	10 mos	Abdominal swelling + haematuria	Feb. 1964	Left: Invasion of vessels Right: Fixation, inoperable	Nephrectomy + irradiation, 2000 rad Actinomycin D Biopsy + irradiation, 2000 rad Actinomycin D	Sept. 1965	? Primary tumour Metastases
♀	4 yrs	Abdominal swelling	Dec. 1965	Left: Invasion of vessels, lymph node metastases Right: —	Nephrectomy + Actinomycin D Actinomycin D	Dec. 1965	Primary tumour, right. No mestatases Died at operation
♀	4 yrs	Abdominal swelling	May 1965 July 1964	Left: Lymph node and pulmonary metastases Right: Invasion of vessels	Irradiation, 2800 rad, resection Vincristine Nephrectomy + irradiation, 2000 rad. Actinomycin D	May 1966	Primary tumour, left. Metastases
♂	7 mos	Abdominal swelling	March 1967	Left: Generalized disease Right: —	Irradiation, 1000 rad, nephrectomy Actinomycin D Resection + Actinomycin D	May 1967	Primary tumour, right. Metastases

kidney necessitated nephrectomy. The last follow-up performed in March 1970 revealed no evidence of a neoplasm or of renal failure. (Previously published, 13, 27.)

Case 3. Boy, aged 13 months, in whom bilateral nephroblastoma was treated by partial resection of both kidneys; the right tumour was encapsulated and the left penetrated the capsule and invaded the vessels. Actinomycin D was given on the day of the operation and during the next six days. A total of 2 000 and 1 500 rad was delivered to the right and left tumour bed regions, respectively, over a period of four weeks. Left nephrectomy was performed for recurrent tumour ten months later. Oncovin was administered (1 mg weekly) during the next seven weeks. About a year from this second operation there was no evidence of a growth or of impaired renal function. (Previously published, 13, 27.)

Case 4. Boy, aged 1 year, who in 1960 had had right nephrectomy for a nephroblastoma followed by about 2 000 rad to the tumour bed. An abdominal swelling was palpated in the region of the left kidney in 1966 and, after irradiation with a tissue dose of about 1 800 rad, partially resected. The tumour was encapsulated. Actinomycin D and cyclophosphamide medication were administered at regular intervals for about a year. Two years after the last treatment the boy was well, and there were no signs of recurrence, metastases or impairment of renal function. (Previously published, 13, 27.)

More detailed data relating to the non-survivors are presented in Table 3.

There were local recurrences in all 5 patients in whom no postoperative irradiation was applied to the tumour bed and in 6 of the 15 patients in whom irradiation was administered, in 3 after irradiation only (2 200, 2 500 and 1 500 + 1 500 rad) and in 3 patients after resection and postoperative irradiation (2 000, 1 500 and 1 900 rad). The doses to the cured patients were 2 500, 2 000, 4 300 and 1 800 rad.

One patient died at operation, and in another the stage at death was not known. In 6 of the remaining 13 patients the clinical findings suggested that the primary tumour and renal insufficiency were the cause of death; at autopsy the renal outflow tract was obstructed by the growth and no distant metastases were evident. Autopsy in one patient disclosed metastases in the lungs, pleura, liver and cerebellum and a primary growth in one kidney. Distant metastases were present in 8 patients in whom no autopsy was performed; in 3 patients the stage of the primary growth at death was not known. No patient died from renal insufficiency unless there was local recurrence of the neoplasm.

Discussion

Eleven of the 19 patients comprising this material were less than one year old on admission (57 per cent). The peak incidence of nephroblastoma occurred at 2 years. The low age of the patients with the condition, its occasional observation at birth and the relatively high frequency of associated congenital malformation of the urogenital tract point to a foetal origin of the neoplasm. If some

measure of immunologic dependence of this kind of tumour is assumed, it would seem reasonable to ascribe the relatively high incidence of bilateral involvement in this age group to the established low level of the immunologic protection in children below one year of age.

While the difficulty of distinguishing between primary bilateral nephroblastoma and a unilateral growth that has spread to the other kidney is recognized (7, 12, 16, 21, 25, 26), the clinical problems presented by the two conditions are roughly the same, and the two types have therefore been considered as a single group.

The low incidence of bilateral anomalies should always suggest neoplasms as has been pointed out elsewhere (1, 26). Quite a long period elapsed before a diagnosis of malformation was corrected in 3 of the present cases of bilateral nephroblastoma.

The more aggressive treatment of this condition given in the last decade has yielded better results (9, 31), and in recent years there has been a greater number of survivors with bilateral involvement (1, 2, 23). Six children of the present material died from local damage caused by the primary growth (there were no metastases); with more energetic treatment at least some of these lives might have been saved.

A compromise between radical removal of the neoplasm and preservation of renal function must be sought before deciding the treatment to be given in bilateral cases. Few cures have been secured by operation alone (8, 11, 13), and surgery combined with radiation is the treatment of choice. The effect of actinomycin D on the cure rate has yet to be conclusively established (29, 30). Partial nephrectomy may be as effective as total nephrectomy with encapsulated tumours (8, 13, 28). The radiation dose required in bilateral growths is also uncertain. The tolerance of the kidney in children has yet to be ascertained (15, 22, 32). Some relevant figures have been reported for 6 children (17) in whom nephrectomy was followed by irradiation with doses of more than 2 400 rad and who died from renal failure due to radiation nephritis. Doses higher than 2 000 rad have been reported to cause radiation nephritis (6, 19). Recurrences were observed in the present series after irradiation with doses above 2 000 rad. On the other hand, one patient given 4 300 rad to both kidneys still had no evidence of renal failure 3 years later; there are, however, reports of this sequela developing through radiation nephritis as long as twenty years after treatment (14, 15, 18). The results for the present material throw no light on this matter.

The value of preoperative radiotherapy is difficult to establish even in quite large series (24). Of 4 patients with bilateral tumours so treated, 2 were cured and 2 died. (One of these had metastases on admission.) It would seem that the value of preoperative irradiation in diminishing the growth and facilitating

the surgical procedure is even greater in the bilateral conditions; these of course present more severe surgical problems, quite apart from the potential reduction in the number of metastases. For 2 out of 4 surviving patients the treatment consisted in combined bilateral surgery and irradiation, for another survivor partial nephrectomy on one side and bilateral irradiation with high doses, and for the fourth (cured) partial resection 6 years after nephrectomy and irradiation for the primary tumour; all 4 patients received chemotherapy. A combination of surgery and irradiation of both kidneys would seem to be the method of choice. The appropriate surgical procedure must be chosen individually. Since actinomycin D has not been found to impair renal function there would appear to be nothing against its employment (17).

The fact that the results were better for the afflicted children under 1 year of age than for the older ones cannot be easily explained since it is not known whether a specific immunologic response may be more easily induced in infants.

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SUMMARY

A series of 19 patients with bilateral nephroblastoma is presented and some clinical features of the condition, its treatment and the outcome are discussed. The treatment of choice would seem to be radical removal of the two tumours followed by radiotherapy. The role of chemotherapy could not be established.

ZUSAMMENFASSUNG

Eine Serie von 19 Patienten mit bilateralem Nephroblastom wird hinsichtlich der klinischen Erscheinung dieser Krankheit und deren Behandlung und Prognose diskutiert. Die Methode der Wahl scheint radikale Exstirpation der beiden Tumoren mit nachfolgender Bestrahlung zu sein. Über den Wert der Chemotherapie konnte kein Urteil abgegeben werden.

RÉSUMÉ

L'auteur présente une série de 19 malades atteints de néphroblastome bilatéral et examine certains des caractères cliniques de cette affection, son traitement et son pronostic. Le traitement de choix semble être l'exérèse radicale des deux tumeurs suivie de radiothérapie. Le rôle de la chimiothérapie n'a pas pu être établi.

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