# Section of Pædiatrics

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# Papers

## Clinical Observations on the Thalidomide Syndrome

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Children with thalidomide-induced malformations who were born between 1959 and 1961 are now in adolescence. There is necessarily continued preoccupation with their education, vocational training and future independence or supportive care. Their physical defects are well known (Lenz 1962, Lenz & Knapp 1962, Smithells 1973).

Approximately 300 such patients, all the known surviving thalidomide children in Great Britain, have recently been examined for medicolegal purposes. The method of examination and of recording the findings was standardized as far as possible. Work is in progress to analyse the data, and this report is based on a sample of 175 children examined in London, 76 of these by the author. There were a number of previously unreported findings and, since there are parents who believe that their children may be additional thalidomide victims, it is clearly important to record the findings in those children known or strongly suspected to be thalidomide victims.

*Symmetry of Limb Defects*

Some doubt has been expressed regarding whether thalidomide can cause major asymmetry. A minor degree of asymmetry is the rule in experiments on the marmoset and macaque monkey (Poswillo 1976, personal communication). In the Ministry of Health Report on thalidomide (1964) the relative frequency of single-limb defects increased markedly as the likelihood of thalidomide exposure diminished. The incidence of three-limb defects however varied little. In the present sample a single upper limb was affected in 1.2% and a single lower limb in 7.4%, a very similar incidence to the 'known-exposure' group in the 1964 report. Major asymmetry is therefore uncommon as regards single-limb defects, but major differences in severity between two limbs are not rare (Table 1).

*Table 1*

**Symmetry of limb deformity**

| | *Percentage affected on:* | | | |
|---|---|---|---|---|
| | *One side only* | *Both sides asymmetrically●* | *Both sides symmetrically* | *Neither side* |
| Arm | 1.2 | 26.3 | 60.6 | 11.9 |
| Leg | 7.4 | 9.7 | 24 | 58.9 |

● Substantial difference between the two sides

*Delayed Ossification*

We have seen several patients in whom the upper end of the humerus or femur only appeared on X-ray at the age of 10–12 years, suggesting that

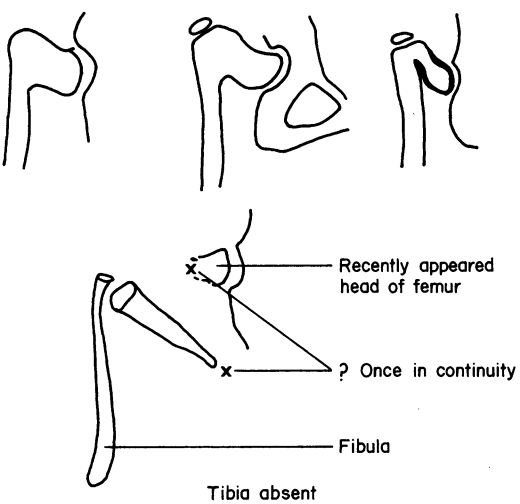


Fig 1 *Delayed ossification. Appearances in 4 children. Possible deformation of late-ossifying cartilage*

there may have been a cartilaginous model present despite apparent absence previously. Muscle pull and weight bearing on such unossified bone could distort the anatomy and even lead to fracture. The variety of angulation observed at the upper end of the femur in different patients and the presence of a late-appearing short upper separate fragment could be explained in this way (Fig 1). Distortion to the point of fracture could therefore be an additional cause of deformity.

*Spinal Defects*

Some spinal changes in thalidomide-affected individuals differ little from the commonly observed changes such as adolescent kyphosis and osteochondritis. However, an otherwise rare and potentially crippling condition is observed in thalidomide victims: a progressive anterior fusion of the lower thoracic and upper lumbar vertebral bodies (Fig 2). In our sample the incidence is 2.8%

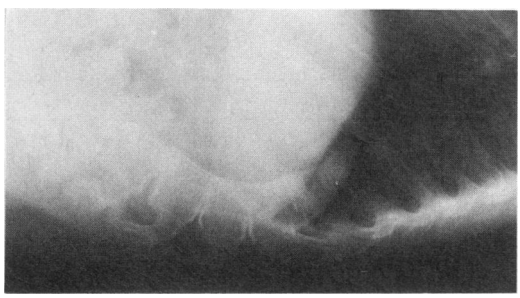

Fig 2 *Thoracolumbar anterior progressive spinal fusion*

and it has occurred in children with severe lower-limb deformity. It may in part represent a stress reaction resulting from abnormal mechanical forces acting on the spine as a result of abnormal mobility patterns. This abnormality has recently been reported by Edwards & Nichols (1975). Increasing stiffness and pain is further limiting what little mobility remains in some patients.

McCredie (1973) reported a 66% incidence of some degree of lumbar spina bifida in 41 thalidomide patients examined radiologically. In our sample there was one case of an open lesion with spina bifida at birth, but the radiological incidence of subclinical lesions has not been examined.

*Growth*

Of 76 patients seen personally, 82% had heights within the normal range between the ages of 12–14 years. The remainder had a stature below the 3rd percentile. In the presence of lower-limb defects we measured sitting trunk height, and found 5 of those with normal, and 5 of those with reduced stature, had spinal defects. Longitudinal studies over 4 years on 28 children, with 3-monthly observations, showed a normal growth pattern with prepubertal acceleration even in short individuals. It appears therefore that dwarfism is determined early, as in many other conditions. Extending the study to 202 recently examined thalidomide-affected children aged 8–14 years confirmed an increased incidence of shortness (Figs 3 and 4).

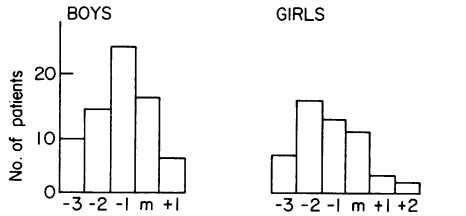


Fig 3 *Standing height of thalidomide-affected children with normal legs (mean (m) with standard deviation)*

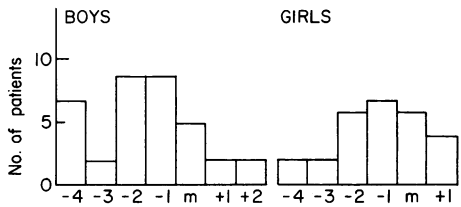


Fig 4 *Sitting height of thalidomide-affected children with abnormal legs (mean (m) with standard deviation)*

*Central Nervous System*

Major eye, ear and cranial nerve defects have been documented (Rafuse *et al.* 1967, Zetterstrom 1966, d'Avignon & Barr 1964, Livingstone 1965, Smithells 1965). Some additional features were encountered in the present study. In some individuals there was an inability to produce tears, or inappropriate lacrimation with salivation (crocodile tear syndrome) occurring together with ear defects and generally, but not always, homolateral facial nerve paralysis. In one patient the pupils were immobile. We encountered ptosis, abducens and rarely oculomotor (partial), facial, and uncommonly palatal paralyses. The facial nerve defects were invariably associated with ear defects and deafness and many of the patients had other cranial nerve lesions as well. Patients with homolateral defect of lateral gaze and deafness had difficulty in not bumping into people in crowds, and could not anticipate being overtaken when riding a bicycle. In a few individuals (1.7%) epilepsy was the dominating handicap. Stephenson (1976) has examined the records of a large group of thalidomide victims, and his findings support our early impression that there may be a greater incidence of central nervous system damage in thalidomide-affected patients than was thought

previously. The cranial nerve and lacrimation defects could be explained by lesions at nuclear level in the midbrain (Table 2).

*Table 2*

**Central nervous system defects**

| | *Percentage incidence* | | |
|---|---|---|---|
| | *Alone* | *+VII* | *+VII bilateral* |
| Ptosis, partial III | 1.1 | | |
| Ptosis, partial III bilateral | 1.1 | | |
| VI | 3.3 | 0.6 | |
| VI bilateral | 4.0 | 6.3 | 2.9 |
| Ptosis + VI | 1.2 | 0.6 | 0.6 |
| VII | 2.2 | | |
| VII bilateral | 3.5 | | |

Absence of tears 2.3%; crocodile tears 6.3%; epilepsy 1.7%; mental retardation 4%.

*Sexual Development*

Genital malformations, such as septate uterus and vagina, and testicular nondescent, have been recorded in some children. Failure of scrotal development was a regular feature in association with severe lower-limb deficiency. However, secondary sexual development is proceeding normally, though puberty is delayed in a small number. Of 41 males examined personally, 70% had normal genitalia (12–14 years), and one of these had lower-limb phocomelia; 30% (12 patients) had unilateral or bilateral undescended testes, together with lower-limb phocomelia in 4, and with less severe lower-limb defect in 3; 9 had upper amelia or phocomelia, both upper and lower-limb defects in some; histology in 4 showed 'normal immature testis' at the time of orchidopexy. Unilateral anorchia may occur with unilateral renal agenesis, as in other instances of congenital malformation, but renal investigations have so far been undertaken only in the event of urinary tract symptoms.

*Independence and Future Outlook*

Fig 5A shows the present situation regarding thalidomide-affected children at home, school, travelling or on holiday. The 'independence grading' of 0–4 signifies normal independence, requiring occasional assistance, requiring assistance several times every day or night, having limited ability for self-help, total dependence on others. Taking the view that severe bilateral upper-limb defect (amelia, short or long phocomelia, radial aplasia with short ulna) is likely to prevent work in a nonsheltered environment, the number likely to be partially or wholly dependent after completing their education rises sharply (Fig 5B). Such projections may be too pessimistic but there is good reason for professional concern. Such concern should nevertheless not neglect further study of the physical effects of thalidomide.

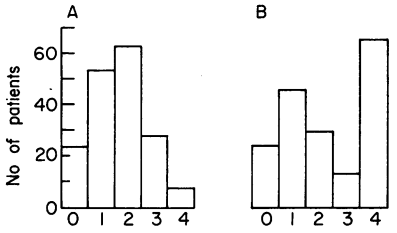


Fig 5 *Independence grading of thalidomide-affected children. 0 = normal independence, 1 = requiring occasional assistance, 2 = requiring assistance several times every day and night, 3 = having limited ability for self-help, 4 = total dependence on others.* A, *present situation.* B, *prediction for future*

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