Lethal acродysgenital dwarfism: a severe lethal condition resembling Smith-Lemli-Opitz syndrome

M LE MERRER*, M L BRIARD*, S GIRARD†, N MULLIEZ‡, C MORAINEL, AND M C IMBERT¶

Summary  We report eight cases of a lethal association of failure to thrive, facial dysmorphism, ambiguous genitalia, syndactyly, postaxial polydactyly, and internal developmental anomalies (Hirschsprung's disease, cardiac and renal malformation). This syndrome is likely to be autosomal recessive and resembles Smith-Lemli-Opitz (SLO) syndrome. However, the lethality and the common occurrence of polydactyly, and the sexual ambiguity distinguishes this condition from SLO syndrome. A review of published reports supports the separate classification of this syndrome for which we propose the name lethal acродysgenital dwarfism.

In September 1985, at the meeting of the European Club of Genetic Counselling, we reported three cases of children with a syndrome reminiscent of the Smith-Lemli-Opitz syndrome. However, it seemed to us to differ from the latter because of the extent of the genital abnormality and the rapidly fatal evolution.† Since then, we have encountered five new cases very similar to the first ones. Independently, Donnai et al.‡ have reported three similar cases. In this paper, we discuss our eight cases and compare them to other published cases. It appears that this syndrome constitutes a new entity which we propose to name lethal acродysgenital dwarfism.

Case reports

Cases 1, 2, 3, 4, 6, and 7 were encountered during genetic counselling sessions. Cases 5 and 8 were ascertained from anatomical and pathological records.

Case 1

Case 1, a female, was the first child of young parents. She was born in the breech position in a state of fetal distress, weighing 2370 g and measuring 44 cm. The face was dysmorphic with a narrow forehead, anteverted nares, broad and prominent nasal bridge, angiooma on the forehead, narrow and antimongoloid palpebral fissures, blepharoptosis, and marked micrognathia. The head circumference was 31.5 cm and the neurological state very poor (fig 1).

In addition, there was bilateral clinodactyly of the five fingers, proximally placed thumbs, and postaxial polydactyly on the left hand. The feet also showed bilateral postaxial polydactyly, with syndactyly of the second and third toes. The fingers and toes were clenched. On examination, she was small for her age with very widely spaced nipples, female external genitalia, and a sacral dimple. No gonads were palpable.

X-ray examination showed a dense base to the skull, thin ribs, and narrow iliac bones. On the left hand, the polydactyly affected the bones and the first metacarpal was short. On the right foot, there were only four metatarsals of which the last two were in the form of a Y thus giving rise to the polysyndactyly. On the left foot, the fourth and fifth metatarsals were joined proximally and the sixth toe had no bone (fig 2).

An examination of the eyes revealed bilateral congenital cataract. The karyotype was marked (46,XY) and revealed the sexual ambiguity.
Lethal acrodysgenital dwarfism

FIG 1 Case 1 showing female external genitalia, polydactyly, low set ears, anteverted nares, broad nasal bridge, and micrognathia.

FIG 2 X-ray of feet of case 1.

CASE 2
The second child of a young couple was born after induced labour at 38 weeks. Ultrasound examination at 35 weeks showed retarded growth which was confirmed at birth (length 40.5 cm, birth weight 2250 g, head circumference 30 cm).

There was marked dysmorphism including an antimongoloid slant of the palpebral fissures, marked micrognathia, and broad alveolar ridges. The tongue had a multicystic appearance and there was excessive skin on the back of the neck. Syndactyly of the second and third toes was noted as well as duplication of the fifth left toe. The child had club feet and dislocated hips. A sacral dimple was present. In the genital region, a voluminous mass was noted, as well as two large folds surrounding a vaginal cleft. No gonads could be palpated.

The child died shortly of respiratory distress. The karyotype was 46,XY.

Necropsy showed an atrial septal defect, a unilobar left lung, and a rudimentary uterus with two well formed fallopian tubes; the gonads had undergone male differentiation.

CASE 3
This child was of indeterminate sex, born at 35 weeks, in the incomplete breech position, birth weight 2180 g, length 43 cm, head circumference 30 cm. The father and mother were 20 and 21 years old, respectively. The dysmorphism consisted of microcephaly with brachycephaly, poorly formed ears, a flattened nose with anteverted nares, cleft suspected until then. The child died of pulmonary complications on day 45.

Necropsy showed an ectopic left kidney, dilatation of the cavities of the right heart, and a macrophagic infiltration of the lungs. The uterus was absent but there were two male gonads and an epididymis. Histologically, the seminiferous tubules were immature and the interstitial cells were poorly developed.
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palate, and flat angiomas on the forehead and eyelids. All four extremities were abnormal: a bilateral vestigial sixth finger implanted in the proximal phalanx of the fifth finger, a sixth toe, and syndactyly between the second and third toes. There was talipes valgus and the cry was weak. The karyotype was 46,XY and the child died on day 24.

Necropsy showed hypertrophic left cardiac cavities, small and immature lumbar-pelvic intra-abdominal testes, Müllerian remnants behind the bladder, and dilatation of the lateral ventricles.

CASE 4
This was a first child born at 35 weeks in the breech position, with slight intrauterine growth retardation (length 46 cm, birth weight 2800 g, head circumference 33.5 cm). The parents were both 34 years old. The child presented the characteristic Smith-Lemli-Opitz facial dysmorphism, associated with a cleft palate, postaxial hexadactyly of all four limbs (fig. 3) with syndactyly of the second and third toes, and a bilateral simian crease. The external genitalia were very hypoplastic, but male (fig. 5). The karyotype was 46,XY.

The child died on day 16. Necropsy showed absence of internal male genital organs and the presence of a common mesentery and infiltration in the lungs.

CASE 5
The discovery of oligohydramnios and of major hypotrophy led to termination of pregnancy at 29 weeks. The fetal karyotype was 46,XY. The external genitalia were female with a blind vagina. At necropsy, severe micrognathia, slanted palpebral fissures, and bilateral urethral duplication were noted. There were no fallopian tubes, uterus, or ovaries, but there were two small abdominal masses resembling testes and a common mesentery.

CASE 6
This child was both small for dates and premature (born at 30 weeks), birth weight 1850 g, head circumference 29.5 cm (<25th centile). She was born by caesarian section because of breech position and multiple malformations. She was phenotypically female and showed micrognathia, broad nasal bridge, antverted nares, a high palate, and horizontal palpebral fissures. The neck was short with an apparent excess of skin. The limbs seemed short with club feet, postaxial hexadactyly.
of the left hand and foot, and syndactyly of the second and third toes. A sacral dimple was noted. Necropsy showed pulmonary hypoplasia and an interventricular septal defect. The gonads resembled testes but there was a very hypoplastic uterus. The right kidney was small and ectopic. The karyotype was 46,XY, inv(9).

Case 7
This small for dates female child, born at term (birth weight 2480 g), was admitted to hospital because of her dysmorphic appearance characterised by micrognathia, a flattened nasal bridge, an arched palate, low set and poorly formed ears, postaxial polydactyly of all four extremities, and hypertrophic labia majora. The neck was short with excess loose skin (fig 6). X rays revealed a sixth lumbar vertebra (sacral dimple), confirmed the polydactyly (synostosis of the fifth metacarpal), and showed a short first metacarpal and brachymesophalangy of the sixth. The child died of heart failure with a patent ductus arteriosus. Necropsy showed large and lobular kidneys. The karyotype was 46,XX.

Case 8
This girl was born to a 17 year old mother of gypsy origin whose parents were consanguineous, but whose precise relationship was not known. As early as the 20th week, ultrasound suggested a low weight gain which was confirmed at birth (birth weight 2050 g, head circumference 31 cm, length 42 cm). She presented with multiple congenital abnormalities and died after 16 days of life.

The karyotype was 46,XY. The face showed characteristic dysmorphology with cataracts and a cleft palate. Postaxial polydactyly was noticed on the hands and feet with a bilateral simian crease and syndactyly of the second and third toes. The external genitalia were female with hypertrophic labia majora and clitoris. The gonads could not be seen.

Necropsy revealed testes in the inguinal canals and a vagina devoid of Müllerian duct derivatives. There were no other anomalies of the internal organs with the exception of a retro-oesophageal subclavian artery and a patent ductus arteriosus. On examination of the skull, slight distension of the lateral ventricles and heterotopic cell clusters were observed. The pancreas appeared immature with large islets of Langerhans.

Discussion
The eight infants we have described obviously show the same pattern of malformations. The major element consists of the genital anomalies with an XY karyotype but complete failure of masculinisation of the external genitalia or even a true sex reversion. The testes were undescended, small, and appeared immature. The presence of a hypoplastic uterus or Müllerian remnants was noted in four out of the seven cases with a male karyotype.

In addition to these genital anomalies, facial
TABLE 1 Features of lethal acrodysgenital dwarfism.

<table>
<thead>
<tr>
<th>Chromosomes</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
<th>Case 6</th>
<th>Case 7</th>
<th>Case 8</th>
<th>Total</th>
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<td>F</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>F</td>
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<tr>
<td>Immature</td>
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<td></td>
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<td>+</td>
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<td>2250</td>
<td>2180</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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</tr>
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<td>Micrognathia</td>
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<td>+</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>+</td>
<td>+</td>
<td>+</td>
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<td>+</td>
</tr>
<tr>
<td>Simian crease</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>Club foot (valgus)</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>Sacral dimple</td>
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<td>+</td>
<td>+</td>
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<tr>
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<td>+</td>
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<td>+</td>
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<td>+</td>
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<td>Urinary tract malformation</td>
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<td>+</td>
<td>+</td>
<td>+</td>
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</table>

The formation of the so-called Ullrich-Feichtiger syndrome 'typus rostockiensis', such as those of Weber and Schwarz, appear to be quite similar to ours. Certainly, the Ullrich-Feichtiger syndrome has been found to be extremely heterogeneous. In Feichtiger's initial observations (1943) the 'Würzburg' type is similar to trisomy 13 or Meckel syndromes, whereas the 'Rostock' type, which is characteristic of this syndrome, is similar to what is currently designated the Townes-Brock syndrome. The existence of this syndrome was questioned as early as 1975 by Pfeiffer and Slavaykoff. They described a sister and brother who died after only a few days of life, both presenting with postaxial polydactyly, the boy also having hypoplasia. While considering the possibility of Ullrich-Feichtiger syndrome, these authors concluded that it was more likely to be Smith-Lemli-Opitz syndrome. Other more recent observations mention Smith-Lemli-Opitz syndrome with early lethality, in which the severely affected phenotype is accompanied by polydactyly. Based on their personal experience and other published reports, Cherstvoy et al. found a significant difference between the Smith-Lemli-Opitz cases that are associated with polydactyly and those that are not. The former seem to constitute a separate entity, characterised in particular by an earlier death, a higher frequency of renal anomalies, and different cerebral malformations. Coincidental with our first three observations, Donnai et al. published three cases in which the
Lethal acrodys genital dwarfism

symptoms were comparable to those described here, and with which they associated other published cases. These authors differentiated these cases from the Smith-Lemli-Opitz syndrome as described in 1964. Indeed, if delayed development and the characteristic facial dysmorphism are also present in the SLO syndrome, the most constant features are hypospadias or cryptorchidism or both in the male, without complete failure of masculinisation, and syndactyly between the second and third toes with or without club feet and metatarsus varus. Polydactyly is seen only exceptionally and early death only occurs in 20% of the cases.

In the light of our observations, the diagnosis of Smith-Lemli-Opitz syndrome in these unusual forms seems to us to deserve close scrutiny. This is confirmed by our analysis of 47 cases published under this title and analysed according to the criteria of lethality or presence of polydactyly.

Of these cases, 20 children out of 47 died in the first few months of life and their phenotype was different to that of survivors. Facial dysmorphism did not differ significantly between the two groups, but cleft palate was present in half the cases, and enlargement of the alveolar ridges was more frequent. On the other hand, postaxial polydactyly, most frequently affecting all four limbs, and marked sexual ambiguity seemed to be characteristic of the lethal forms (73% against 11% and 71% against 0%, respectively). Malformations of the internal organs were also more frequent, and were in themselves a measure of severity: cardiac malformations of all types, uni- or bilateral renal hypoplasia, and more particularly Hirschsprung’s disease were present in eight out of the 20 fatal cases (table 2).

If we follow Cherstvoy et al. and classify the 47 reviewed cases of Smith-Lemli-Opitz syndrome into two groups, ‘with polydactyly’ and ‘without polydactyly’, it appears quite clear that the sexual ambiguity is more severe when there is polydactyly and the prognosis then seems to be extremely poor (table 3).

This analysis indicates the need to differentiate the Smith-Lemli-Opitz syndrome from those cases with polydactyly, marked sexual ambiguity, and early death. The results of family studies contribute a further element to support this division. It has been established that the pattern of inheritance of the Smith-Lemli-Opitz syndrome is autosomal recessive, and this is confirmed by the consanguinity found in certain families and the existence of multiple affected sibs. Within families, the degree of severity is very similar, as one would expect according to genetic heterogeneity. A possible exception is family 1 reported by Dallaire, in which two seriously affected children had severe polydactyly, the third child having no polydactyly. In this family, described in 1969, the author mentions an abnormally long chromosome 16 in the mother that was also present in some of the normal children as well as in some of the affected ones. Without sufficiently precise karyotype studies (marker studies) there remains doubt about the validity of the diagnosis.

**NEW PATTERN OF MALFORMATIONS**

We can therefore distinguish the Smith-Lemli-Opitz syndrome from the new pattern of malformations reported here, which is also transmitted in an autosomal recessive fashion, and which we propose to name lethal acrodys genital dwarfism.

Apart from our eight observations and the three reported cases of Donnai et al., and very recently the case of Scarbrough et al., we can include in this

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**Table 2** Smith-Lemli-Opitz syndrome: two forms?

<table>
<thead>
<tr>
<th></th>
<th>'Classic' (n=27)</th>
<th>'Severe' (n=20)</th>
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<tbody>
<tr>
<td>Genitalia</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>Ambiguous or female</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Cryptorchidism, hypospadias</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>Extremities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postaxial polydactyly</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>Short thumb</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Syndactyly of toes</td>
<td>25</td>
<td>19</td>
</tr>
<tr>
<td>Face</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microcephaly</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>Micrognathia</td>
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<td>19</td>
</tr>
<tr>
<td>Cleft/high palate</td>
<td>9</td>
<td>16</td>
</tr>
<tr>
<td>Antevorted nares</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>Broad alveolar ridges or cyst</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Malformation of internal organs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac defect</td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td>Kidney anomalies</td>
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<td>'Pneumopathy'</td>
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<td>8</td>
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<tr>
<td>Hirschsprung's disease</td>
<td></td>
<td>8</td>
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</tbody>
</table>

*Microcephaly and broad alveolar ridges were not quoted in all observations published.

**Table 3** Smith-Lemli-Opitz syndrome: heterogeneity.

<table>
<thead>
<tr>
<th></th>
<th>Sexual ambiguity</th>
<th>Early death</th>
<th>Pulmonary abnormality</th>
<th>Malformation of internal organs</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=47</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With polydactyly (n=17)</td>
<td>83</td>
<td>70</td>
<td>70</td>
<td>75</td>
</tr>
<tr>
<td>Without polydactyly (n=20)</td>
<td>10</td>
<td>25</td>
<td>10</td>
<td>50</td>
</tr>
</tbody>
</table>

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J Med Genet: first published as 10.1136/jmg.25.2.88 on 1 February 1988. Downloaded from http://jmg.bmj.com/ on October 5, 2023 by guest. Protected by copyright.
entity the cases of Kohler,11 Kretzer et al.,10 cases 1 and 4 of Cruveiller et al.,15 Lipson and Havens,17 Akl et al.,14 Kim and Bootwell,22 Zizka et al.,9 Greene et al.,8 Lowry,29 and Pfeiffer and Slavaykoff.6 The cases of Chernstov et al.12 and of Finsky and DiGeorge16 are closer to the classical Smith-Lemli-Opitz syndrome. If the lack of karyotype makes us doubt the earlier observation of Weber and Schwarz3, we think we can retain the case of Patterson et al.25 in spite of the lack of polydactyly; the phenotype is female whereas the karyotype is 46,XY, the severe dysmorphology is comparable, there is excessive skin around the neck, flexion contractures of the fingers, elbows, knees and hips, and Hirschsprung’s disease. This last point deserves comment. Intestinal ganglioneuroma, responsible for Hirschsprung’s disease and found in eight cases, is a very unusual finding in syndromes of multiple congenital abnormalities and appears to be very specific. The same is true for the persistence of Müllerian remnants11,13,25 (our cases 2, 3, and 6). Finally, a number of other anomalies can be mentioned including cysts of the mouth and tongue, particular histological lesions of the pancreas, and cataracts10,13 (our cases 1 and 8).

The Differential Diagnosis
We question the ‘new lethal syndrome’ of Rutledge et al.60 described by Donnai et al.13 If most of the abnormalities are compatible with the pattern of malformations that we describe, others are not: agenesis of the biliary vesicle, microglossia, and findings from bone x rays determine a slightly different pattern of malformations. The authors recognise that if certain signs were also found in Kohler’s case, others, such as severe mesomelic dwarfism, distinguish it totally.

Similarly, the C syndrome,31 Hall-Pallister syndrome,32 and the hydroelethalus syndrome are easily eliminated, since the acrodyssgenital dwarfism described here lacks the signs specific to each of them, namely trigonocephaly for the C syndrome, hamartomas for the Hall-Pallister syndrome, and hydramnios and hydroelethalus for the hydroelethalus syndrome. In the same way, the absence of kidney and liver cysts excludes the diagnosis of Meckel’s syndrome. However, in a commentary on the variability of the Smith-Lemli-Opitz syndrome, Lowry et al.18 questioned whether in similar cases these features could not result from Meckel’s syndrome. This seemed to him to be possible in view of the absence of renal lesions, or alternatively they could be a variant of the Smith-Lemli-Opitz syndrome. The lethal acrodyssgenital dwarfism syndrome is an answer to their question.

Trisomy 13 is the only other possible differential diagnosis and in this case simple karyotype analysis must be performed systematically to exclude this.

Genetic Counselling
The familial observations concerning two sibs,6,11 and the parental consanguinity found in the case of Akl et al.14 and our case 8, are arguments in favour of an autosomal recessive pattern of inheritance and indicate that caution is required in genetic counselling. Prenatal diagnosis would entail a decision on the chromosomal sex (fetal karyotype) and the appearance of the fetus on prenatal ultrasonography.

Conclusion
In spite of the resemblances and of the difficulties in classifying certain cases in one category or the other, we feel justified in proposing a new syndrome, lethal acrodyssgenital dwarfism, which is different from the Smith-Lemli-Opitz syndrome, with the reservations imposed by the lack of information concerning the mutations responsible, which may or may not be allelic.

We would like to thank J Canet, Centre Hôpitalier Intercommunal de Créteil, and M Tournaire, Hôpital Saint-Vincent de Paul de Paris, for their data. We are grateful to Professor J Frézal and Dr P Maroteaux for their help. We also thank Gisèle Gaud for secretarial assistance.

Addendum
After this paper had been submitted for publication, a report appeared in the American Journal of Medical Genetics in which Cynthia Curry described 19 children with a syndrome called Smith-Lemli-Opitz type II. All the features described in the above report provide further evidence of the existence of a discrete phenotype, more severe than the Smith-Lemli-Opitz syndrome and to be distinguished from it. Curry’s observations are fully consistent with those described in our paper. For all these reasons it could be misleading to lump this entity together with the original SLO syndrome. Although, as outlined in the American Journal of Medical Genetics editorial comment, the possibility of allelic mutation cannot be excluded, it seems better, at least on clinical grounds, to distinguish two syndromes. Accordingly, and bearing in mind the main differential features in our cases, as well as in those of Curry and Donnai et al, we propose to name this syndrome the lethal acrodyssgenital dwarfism syndrome.
Lethal acrodysgenital dwarfism

References


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