Virchows Arch [Pathol Anat] (1984) 404:413–425

Virchows Archiv A

The smith-lemli-opitz syndrome

A detailed pathological study as a clue to a etiological heterogeneity

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Summary. An analysis of 33 autopsied cases with the Smith-Lemli-Opitz syndrome (including 8 cases from our practice) is presented. Polydactyly in dead SLOS children was found in 51% (17/33) of cases and occurred significantly more often in this group than in the whole group of SLOS (20–22%). Certain morphological differences in the type of renal, cerebral, pulmonary and pancreatic anomalies indicate the existence of two phenotypically similar SLOS: 1) with polydactyly; 2) without it. The presented data initiate SLOS heterogeneity.

Key words: The Smith-Lemli-Opitz syndrome – Polydactyly – Autopsy – diagnosis – Congenital malformations

Introduction

The Smith-Lemli-Opitz syndrome (SLOS) is an entity well known to pediatricians and genetists. A series of comprehensive reviews with complete clinical and genetic data on the disease have been reported (Johnson 1975; Jeanty et al. 1977). Meanwhile, the data on pathological manifestations of the syndrome are relatively scanty. According to Lowry (1983) about 20 autopsied cases have been reported and have been few attempts to systematize the available scattered data.

Kohler (1983) presented 2 siblings with the SLO syndrome where polydactyly was associated with cardiac and renal anomalies and peculiar changes of pancreatic islets. His study has encouraged us to analyse all reported autopsied cases (including our findings) having sorted them into 2 groups: 1) with polydactyly, 2) without polydactyly.

The main purpose of this work is a comparison of morphological findings in both groups of the affected patients.

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Material and methods

Eight autopsied SLOS cases from our practice (two of which have been previously reported by Cherstvoy et al. (1975)) and 25 autopsied cases from the literature (Fine et al. 1968; Lowry et al. 1968; Dallaire 1969; Opitz et al. 1969; Schumacher 1969; Robinson et al. 1971; Srsen 1972; Garcia et al. 1973; Akl et al. 1977; Cruveiller et al. 1977; Dzarlieva et al. 1977; Fierro et al. 1977; Bene et al. 1980; Kretzer et al. 1981; Kohler 1983; Žižka et al. 1983) we reviewed. In our material 6 of 8 children died up to 7 days, one child died at $3^1/_2$ months and one at 17 months.

The morphological study was performed by well accepted methods, the only exception was an additional detailed study of muscles, vessels and nerves. The brain was examined histologically using Nissl and Kajal stainings. The pancreatic islets were stained by aldehyde-fuchsin and in the other cases haematoxylin and eosin staining prevailed.

All SLOS cases were sorted into 2 groups: "with polydactyly" and "without polydactyly". Polydactyly was revealed in 5 of 8 our cases and in 12 out of 25 cases reported in the literature. In total we have the data on 17 dead SLOS children with polydactyly and 16 without polydactyly.

Results and discussion

The association of facial and cranial anomalies contributes a rather peculiar phenotypic appearance to SLOS children. In our patients epicanthus was found in 5/8 cases, antimongoloid slanting of the palpebral fissues – 2/8, broad nasal bridge – 6/8, "anterverted" nostrils – 7/8, cleft palate – 4/8, broad maxillary alveolar ridge – 8/8, microgenia – 6/8 (Fig. 1.).

To clarify the details and the genesis of some limb anomalies we have studied 8 upper limbs of 4 polydactylic children (dissection of muscles, nerves, vessels and bones). The range of anomalies appeared to be rather wide (Table 1).

The humerus and ulna were found to be slightly shortened (6/8). Four upper limbs had synostosis (lack of separation) of os lunatum and os triquetrum as well as of os capitatum and of the carpus. All upper limbs presented slightly deformed articular surfaces of humeri, forearm and finger bones and rigidity of the anterior portion of elbow joint capsule and palmar portion of proximal interphalangeal joint capsule. The changes in the muscles are grouped in the following: 1/ aplasia of some muscles (ulnar head of the m. pronator teres – 6/8; m. flexor carpi ulnaris – 2/8; m. palmaris longus – 6/8; m. policis extensor brevis – 4/8); 2/ supernumerary muscles (the third head of biceps – 8/8; m. coracobrachialis – 6/8; m. extensor digity III – 8/8; 3/ other anomalies and variants of the structure (incomplete division of certain muscles, extra portions of the muscle belly or tendon, hypoplasia, anomalous fixation and functional defective length) were found in almost all of the muscles., in the forearm and wrist in particular. Meanwhile, functional defective length (the discrepancy between muscle length and the length of the corresponding segment of the limb) of muscle flexors of the forearm and fingers was constantly revealed. Such shortening of the muscle flexors seems to form the basis of the flexor contractures of the upper limbs and, probably, of the deformities of the joint surfaces in bones. The latter, in their turn, might influence the formation of these contractures.

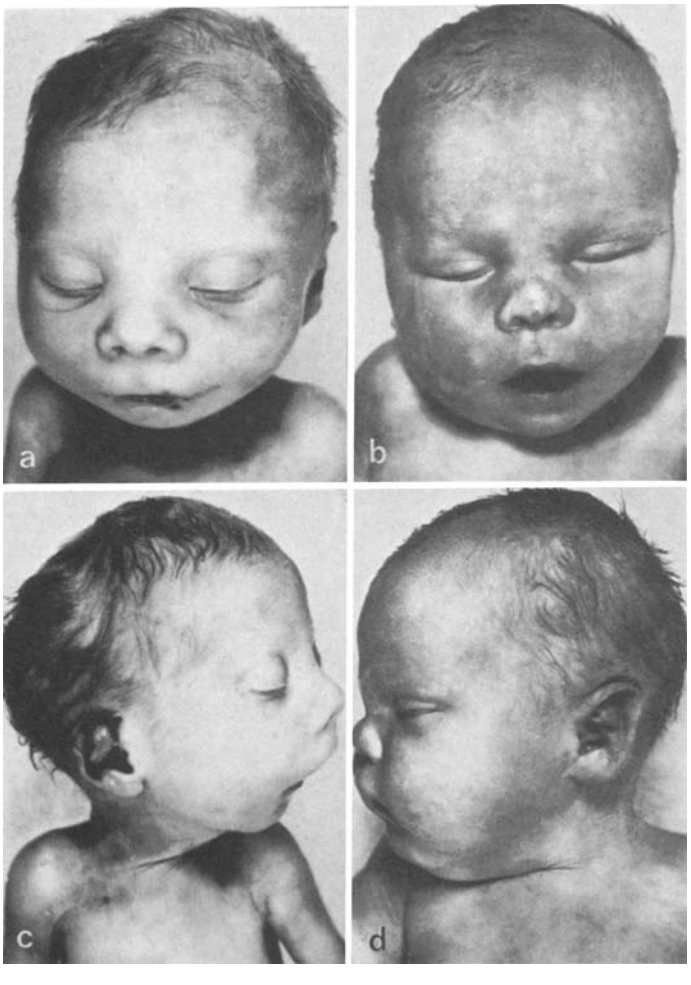

Fig. 1 a–d. Peculiar facies of SLOS children: **a** an infant dyiing at the age of 9 days without polydactyly. **b** a polydactylic neonate who survived only one hour (frontal views). **c, d** the same as above in profiles

The anomalies of vessels and nerves were extremely variable (different levels in division of a. brachialis into radial and ulnar, persistence of anterior interosseal artery and the absence of a normal superficial palmar arch). Unstable level in nerve formation of brachial plexus, aplasia of musculocutaneous nerve (2/8) or variability in its structure (6/8) were also found; the branches to VI finger originated from the ulnar nerve.

Thus, the data presented here show that in SLOS cases many anatomical structures are anomalous to some extent (Fig. 2). Some of the mentioned anomalies are probably due to a direct effect of the anomalous gene or genes on the morphogenesis of certain anatomical components of the limbs. The other anomalies are, probably, secondary and due to primary morpho-

Table 1. Limb anomalies in the SLO syndrome

N	Type of anomaly	Incidence			
		Bila-teral	Unilateral		Total
			Left	Right	
The upper limbs					
1.	Micromelia	5	–	–	5
2.	Polydactyly (postaxial) including:	3	1	1	5
	a) polydactyly type A	3	1	–	4
	b) polydactyly type A with VI metacarpal bone	2	1	–	3
	c) polydactyly type B	–	–	1	1
3.	Synostosis of V–VI metacarpal bones (Y-shaped)	1	–	–	1
4.	Brachydactyly	1	–	–	1
5.	Clinodactyly of V finger	1	–	–	1
6.	Contracture of the elbow	5	–	–	5
7.	Flexion contracture of fingers including ulnar deviation of the hand	1	–	–	1
The lower limbs					
8.	Polydactyly including	1	2	1	4
	a) fibular polydactyly type A	1	1	–	2
	b) fibular polydactyly type B	–	–	1	1
	c) tibial polydactyly (double 1 toe)	–	1	–	1
9.	Syndactyly including	5	2	–	7
	a) partial syndactyly IV–V	1	–	–	1
	b) partial syndactyly II–III	3	–	–	3
	c) complete syndactyly II–III	1	1	–	2
	d) partial syndactyly V–VI	–	1	–	1
10.	Hypoplastic calcanean tuber	1	–	–	1
11.	Short thick great toe	2	1	–	3
12.	Limited extension of the hip	2	–	–	2
13.	Club foot	1	–	1	2
14.	Pes varus	–	–	1	1
15.	Pes valgus	1	1	–	2

genetic disturbances. Flexor deformities of the upper limbs, observed in this syndrome, are due to the anomalies of many anatomical structures, though the main role in their pathogenesis is probably played by the shortness of certain flexors, since the flexion degree of certain joints was consistent with the defective length of the muscles.

The anomalies of CNS are presented in Table 2. There are no significant differences in the incidence and structure of CNS anomalies in 2 SLOS groups apart from a higher occurrence of microcephaly and hydrocephaly in the group of dead patients without polydactyly. The anomalies of the corpus calosum and gyri in the cerebral hemispheres are typical in both SLOS forms (Fig. 3a, b).

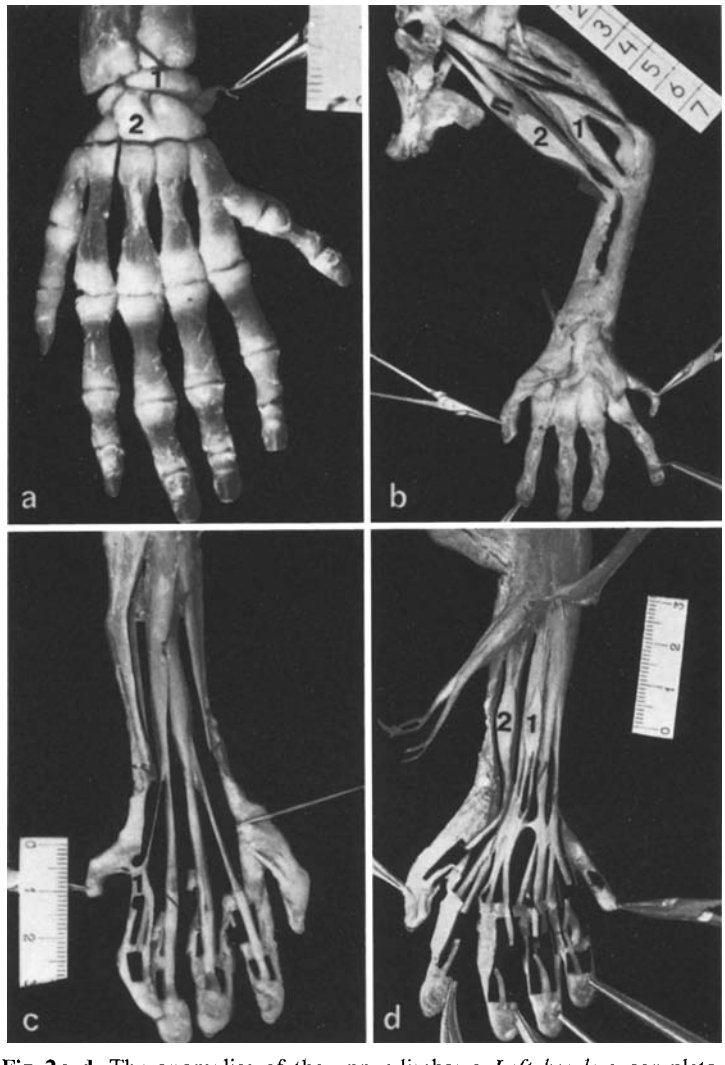

Fig. 2a–d. The anomalies of the upper limbs: **a** *Left hand:* a complete synostosis of the os lunatum and os triquetrum (*1*), partial synostosis of the os capitatum and os hamatum (*2*), of the 5th and 6th metacarpal bones, postaxial polydactyly type A. **b** Right upper limb: functional defective length of mm. brachialis (*1*) and biceps brachii (*2*), which flex the forearm. **c** The muscles of the anterior portion of the forearm (superficial layer). Hypoplastic tendon of superficial flexor of the 5th finger and its anomalous structure – tendon dilation in metacarpophalangeal joint (*1*) and in VI finger. The latter tendon bends finger VI. Aplasia of m. palmaris longus **d** The muscles of the anterior portion of the forearm (*deep layer*), superficial muscles are cut and placed aside. The tendons of m. flexor profundes (*1*) of 2–5 fingers and the tendon of m. flexor pollicic longus (*2*) are cut to eliminate finger flexion (obviously notable shortened length of the tendons). A double distal part of the 2nd lumbrical muscle (*3*)

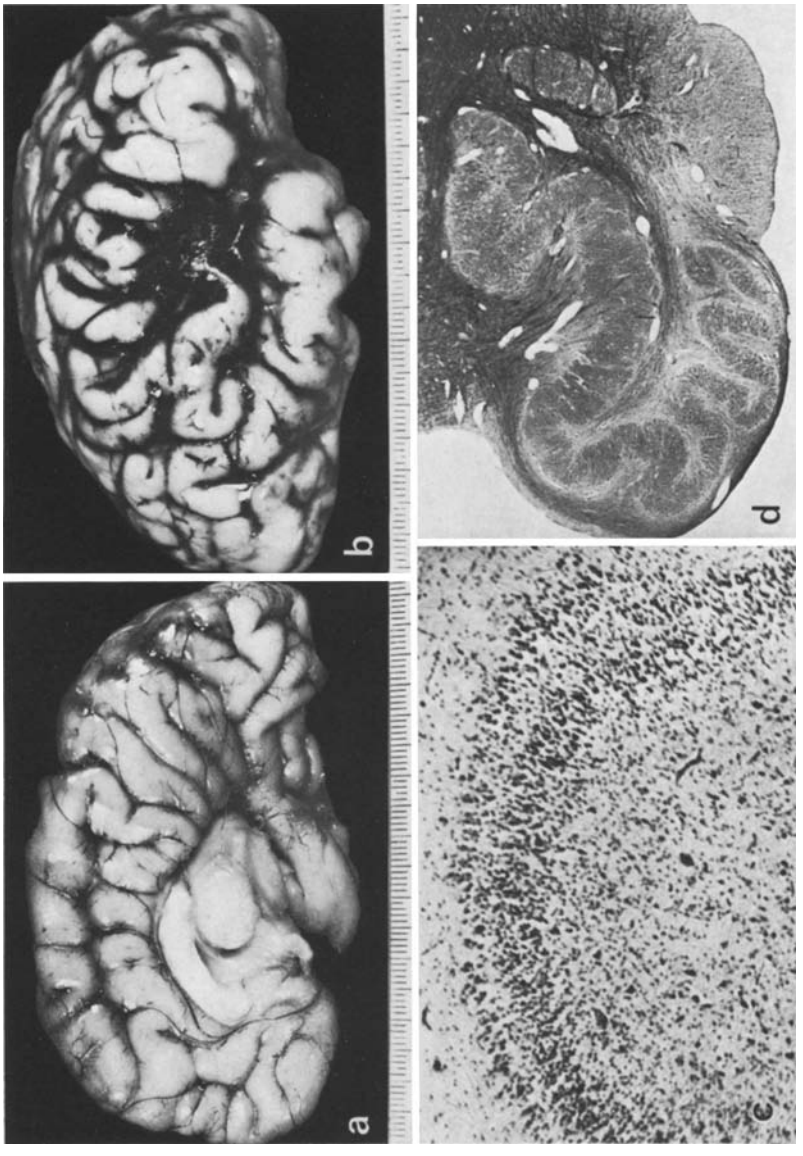

Fig. 3a–d. CNS defects and anomalous structure of hippocamp and medulla oblongata at SLO syndrome with polydactyly. **a** Aplastic splenium of the corpus callosum. **b** Hypoplasia of the 1st temporal gyrus. **c** Focal duplication of dentate fascia of the Ammon's horn (Haematoxylin-Eosin, ×27). **d** Dysplastic lower olivary nuclei (Kajal, ×15)

A detailed histological study of CNS was performed only in 6 cases (Table 3). From Table 3 it is clear that the cerebral cortex generally preserves a regular laminar structure but with a number of anomalies (features 1–5). The structural anomalies of the hippocampus include irregularly shaped fascia dentate with patchy twolayered structure, slitting off neurons from the fascia dentate and neuronal loss and disturbed orientation in the H_2 field of Ammon's horn (Fig. 3c). The olivary nuclei of the medulla oblongata were dysplastic (Fig. 3d). Structural disarrangement of the cerebellum

Table 2. Congenital malformations of CNS in the SLO syndrome

Anomaly	With polydactyly							Without polydactyly					Total
	1	5	6	7	8	Literature data	Total	2	3	4	Literature data	Total	
Microcephaly	−	+	+	+	+	1/11	5/16	−	+	−	12/13	13/16	18/32
Hydrocephaly	−	−	−	−	−	1/11	1/16	−	+	−	3/13	4/16	5/32
Hypo/aplasia of the corpus callosum	−	+	−	+	−	0/11	2/16	+	+	+	1/13	4/16	6/32
Hypoplastic frontal lobes	+	−	−	+	−	1/11	3/16	−	−	+	2/13	3/16	6/32
Dysplastic cerebral gyri	+	+	+	−	+	4/11	8/16	−	−	−	2/11	2/16	10/32
Cerebellar abnormalities	−	+	+	−	−	2/11	4/16	−	−	−	4/11	4/16	6/32
Spinal abnormalities	−	−	−	−	−	1/11	1/16	−	−	−	3/11	3/16	4/32

was manifested by extopic Purkinje cells in the inner granular layer and white matter with subsequence formation of numerous foci in the latter (Fig. 4a). In two cases the cells of the embryonic layer were found in the area of the dentate nucleus (Fig. 4b). Dystopic dysplastic gyri in the white matter of the cerebellum were revealed in only one of 6 cases.

Unfortunately, we can not compare histological anomalies in various parts of the brain with the literature findings, because a complete studies are reported only in the papers by Opitz et al. (1969), Garcia et al. (1973) and Fierro et al. (1977).

The above mentioned studies show some differences between two forms of the syndrome as regards the structure of the cerebral cortex, hippocampus and dentate nuclei of the cerebellum. Disturbed neuronal migration in the cerebral cortex (neuronal presence in the first layer and white matter, reduced neurons in the third layer) (Fig. 4c, d, e), the anomalies of Ammon's horn and the dentate nuclei of the cerebellum are clearly evident in dead children with polydactyly.

In dead SLOS children various heart defects (Table 4) are recorded in 71,8%. In this study congenital heart disease was ascertained in 6 of 8 cases. It included atrio-ventricular communication (2), interatrial septal defect (2), in one case it was associated with stenosis of the aortic ostium and its dextraposition, isolated stenosis of the aortic arch (1), a patent ductus arteriosus (1). Histological findings were non-centributory concerning only circulatory disturbances, cellular degeneration, and in some cases hypertrophy of muscle cells in the ventricles.

The types of heart defects and the abnormalities of great vessels did not differ significantly in two forms of the syndrome, but the anomalies

Table 3. Histological changes in CNS in 6 SLOS cases

N	Structural anomalies	Our cases						Total
		2[a]	4[a]	5	6	7	8	
1.	Mature and immature neurons in the 1st layer	−	−	+	+	+	+	4/6
2.	Neuronal loss in the 3rd layer	−	+	+	+	+	+	5/6
3.	Disturbed neuronal orientation in the 3rd and 5th layers	−	−	+	−	+	+	3/6
4.	Neurons in the white matter	−	−	+	+	+	+	4/6
5.	Anomalous form of Betz neurons	−	−	−	−	+	+	2/6
6.	Decreased number of Betz neurons	−	+	+	−	+	−	3/6
7.	Assymmetry of the nuclei ruber	−	−	−	−	+	+	2/6
8.	Dysplasia of inferior olivary nuclei	+	+	+	+	+	+	6/6
9.	Hypoplastic medial olivary nuclei	−	−	+	−	+	+	3/6
10.	Dysplastic fascia dentate	+	+	+	−	−	+	4/6
11.	Splitting off neurons from fascia dentate	−	−	+	−	+	+	3/6
12.	Two-layered fascia dentate	−	−	+	−	+	+	3/6
13.	Neuronal loss in H_2 field	−	−	+	+	+	+	4/6
14.	Disturbed neuronal orientation of H_2 field	−	−	−	+	−	−	1/6
15.	Splitting off neurons from dentate nucleus	−	−	+	+	+	+	4/6
16.	Dysplastic dentate nuclei	−	−	−	−	+	+	2/6
17.	Ectopic Purkinje cells in inner granular layer	−	−	+	+	+	+	4/6
18.	Ectopic Purkinje cells in the white matter	+	−	+	+	+	+	5/6
19.	Ectopic embryonic cells in dentate nucleus	−	+	−	−	+	−	2/6

[a] The cases without polydactyly

of great vessels occurred more often in the patients with polydactyly ($P < 0.01$).

Gastro-intestinal defects in dead SLOS children (rectal atresia or fistula with ventral ectopia of the anus, cystic liver) were found in 9 of 33 cases including 2 our cases. The children in the 2 of our cases had polydactyly. The literature data disclose no difference in gastro-intestinal abnormalities between two SLOS forms (6/17 with polydactyly, 3/16 without polydactyly).

The study of the urinary system in our cases shows distinct differences in children with and without polydactyly (Table 5). In the group of dead children without polydactyly urinary tract defects were revealed in two cases: 1 – lumbar renal ectopia with stenosis of the right pelvico-ureteral

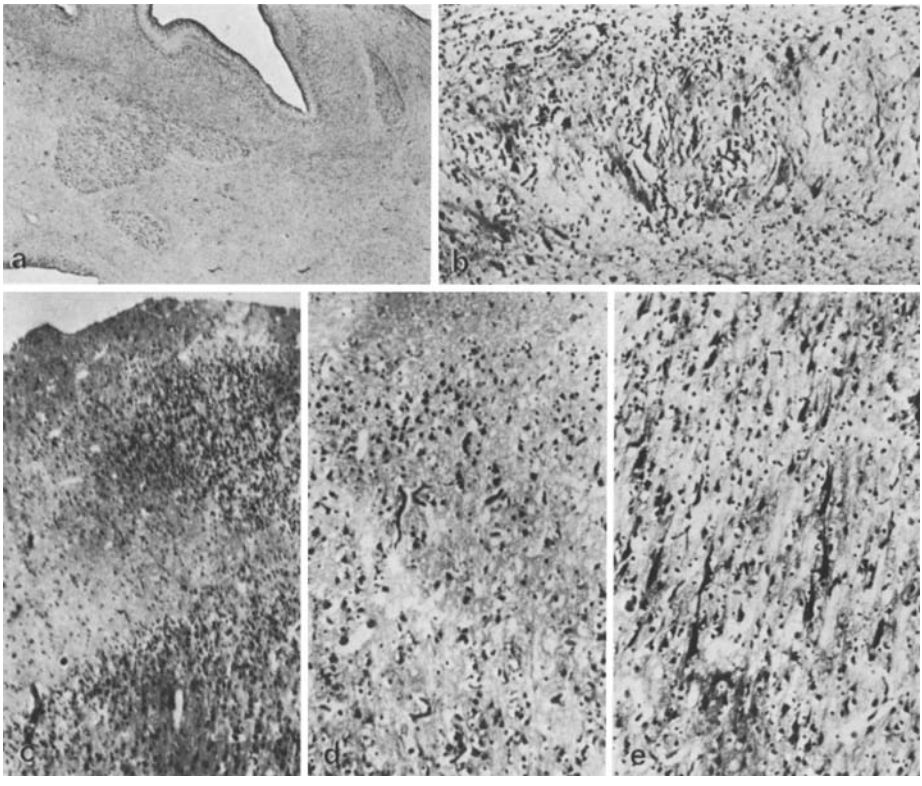

Fig. 4a–e. Histological changes of the cerebellum and cerebral hemispheres in polydactylic SLOS cases. **a** Multiple foci of Purkinje cells in the white matter of the cerebellum (Nissl, ×11). **b** Ectopic cells of external granular layer in dentate nuclei (Nissl, ×63). **c** Field 9, a focus of immature neurons in the first layer (Nissl, ×21). **d** Field 4, focal neuronal loss in the third layer (Nissl, ×70). **e** Field 4, Betz neurons of irregular linear form with hyperchromic curved apical dendrites (Nissl, ×70)

segment, 2 – megaloureter and hydronephrosis. In the second group renal abnormalities were represented by two cases of simple renal hypoplasia with single glomerular cysts and by two cases of cystic changes in the kidneys. In the latter observations one case represented cystic changes interpreted as total dysplasia (hypoplastic variant) (Fig. 5a) and the other case – the initial stage of a macrocystic kidney (an adult type) (Fig. 5b). In the latter case the cortical layer contained a great number of cysts of various sizes, clusters and single. The same cysts were also noted in the medullar layer, in which an evident tubular dilatation was found.

The Table 5 shows that such anomalies as cystic kidneys, renal aplasia or hypoplasia have not been noted at all in cases without polydactyly.

The data on pulmonary anomalies in SLO syndrome are scanty. Only Opitz et al. (1969) and Kohler (1983) reported abnormal pulmonary lobation in polydactylic patients. In our cases no pulmonary anomalies were found

Table 4. Heart defects in dead SLOS children

N	Defect	With polydactyly	Without polydactyly	Total
1.	Interventricular septal defect	4/17	2/16	6/33
2.	Interatrial septal defect	4/17	5/16	9/33
3.	Tetralogy of Fallot	0/17	1/16	1/33
4.	Rudimentary left ventricle	2/17	0/16	2/33
5.	Abnormalities of the great vessels	9/17	2/16	11/33
6.	Patent ductus arteriosus	2/17	4/16	6/33
Total		13/17	11/16	24/33

Table 5. Structure and incidence of urinary tract anomalies in autopsied SLOS cases

N	Anomaly	With polydactyly	Without polydactyly	Total
1.	Polycystic change of adult type or cystic aplasia	6/17*	0/16	6/33
2.	Renal aplasia (hypoplasia)	5/17*	0/16	5/33
3.	Hydronephrosis	0/17	1/16	1/33
4.	Abnormalities of the ureters	1/17	1/16	2/33
5.	Other anomalies	1/17	3/16	4/33
Total		12/17*	4/16	16/33

* p 0.001

in the patients without polydactyly. Out of 5 children with polydactyly two had abnormal pulmonary lobation (in one case lobation was not noted at all, in the other there were 2 lobes on the right with non-lobation on the left). Pulmonary hypoplasia was revealed in two more cases (in one case it was primary and in the other it was due to diaphragmatic hernia). The analysis of our and literature findings showed that in the group of polydactylic children pulmonary anomalies were revealed in 7 of 16 cases, and in the group without polydactyly only in one case.

For a long time no works on the state of endocrine system were published. In 1983 Kohler reported giant cells in pancreatic islets in 2 SLOS cases with polydactyly. This finding allowed Opitz in comments to the paper to suggest that such cells might be a syndrome marker. In our cases endocrine anomalies were noted in 3 cases (all with polydactyly). In two cases we found "giant" cells in the pancreatic islets (Fig. 5c) and in the 3rd case a rare anomaly of the hypophysis – the duplication (Fig. 5d) was found. The question of the specifity of giant cells in SLOS seems doubtful and requires further study, because we noted the same cells in 3 cases of nonclassified complexes of multiple congenital malformations (out of 50 cases).

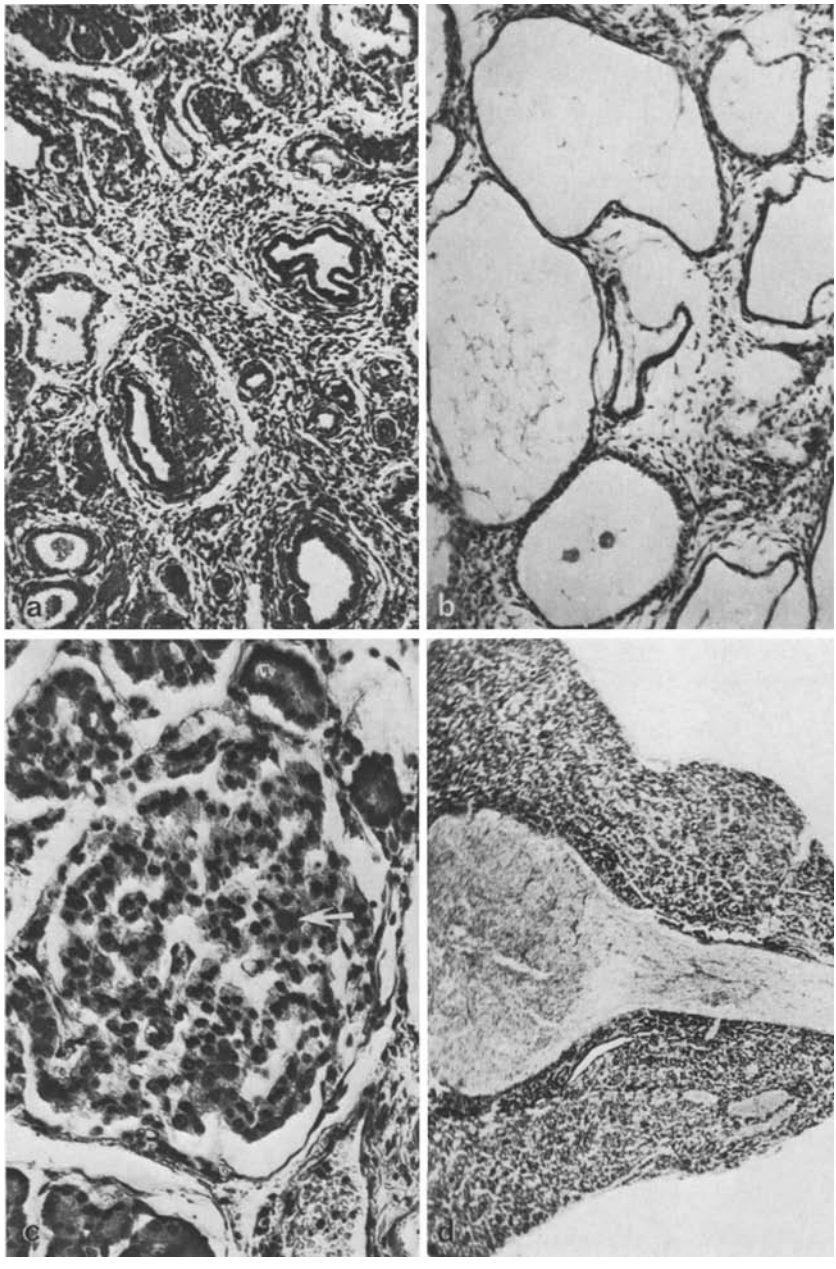

Fig. 5a–d. The anomalies of kidneys, pancreas and hypophysis in polydectylic SLOS cases (Haematoxylin-Eosin). **a** Adult type polycystosis (× 70), **b** Total simple dysplasia (hypoplastic variant) (× 70), **c** A giant cell in pancreatic islets (× 140), **d** Double hypophysis – a broad band of connective tissue which divides 2 adenohypophysial parts (× 70)

Most likely these cells document the increased load on the endocrine function of pancreas in different stress situations.

Several conclusions can be drawn from the analysis of the data:

1. Polydactyly in dead SLOS children occurred in 17/33 (51,5±8,7%) of cases. This figure is certainly higher than for the incidence of polydactyly in all SLO syndrome cases, estumated as 20–22% (Johnson 1975; Jeanty et al. 1977). This finding may demonstrate the higher occurrence of internal abnormalities in SLOS children with polydactyly than in SLOS children without polydactyly.

2. There are differences in the type and incidence of renal, cerebral, pulmonary and pancreatic anomalies in SLOS cases with polydactyly and without it.

3. These facts may serve as an evidence of the existence of two genetically different SLOS forms, which share similar phenotypic manifestations.

Mathematical estimation of the correlation between single phenotypical features is needed for an objective evaluation of the existence or absence of such heterogeneity. The morphological data we present may initiate the analysis of SLOS heterogeneity.

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Accepted July 19, 1984