VARIABLE CLINICAL EXPRESSION OF HOLT-ORAM SYNDROME IN THREE GENERATIONS*

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Holt-Oram syndrome is a distinct autosomal dominant entity presenting with upper limb defects and cardiac abnormality. No correlation between the severity of the heart and the limb defects has been established. Here we report variable clinical expression of Holt-Oram syndrome in three generations. The grandfather presented with typical upper limb defects: phocomelia of arms with three digits on each hand, congenital heart defect and narrow shoulders. His son manifested cardiac conduction disturbance with no congenital heart or skeletal defect. The granddaughter showed ventricular septal defect and moderate radial deviations of both hands with no obvious hypoplasia of the extremities. Clinical data of the presented family suggests lack of penetrance with respect to skeletal and structural cardiac abnormalities in the Holt-Oram syndrome. *Key words: Holt-Oram, syndrome variable expression, congenital heart defects, skeletal malformations.*

The Holt-Oram syndrome (HOS) is an autosomal dominant disorder characterized by upper limb abnormalities and congenital heart defects. The most frequent upper limb abnormality involves the thumbs, whereas secundum atrial septal defect is the most common cardiac malformation. A wide variability of clinical expression of the syndrome has been reported[1-10]. It is accepted that the penetrance of the gene is complete. Known gene carriers have been described without one or the other of cardiovascular or skeletal changes, but not without both. Here we report a family in which the disorder is being transmitted through an obligate carrier, the grandfather to his son and then to the granddaughter. They all presented with variable clinical expressions of HOS.

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Case Report

A pedigree depicting four generations of the index case is shown in Figure 1. The proband (Fig. 1; IV-1), a one-month-old girl born to phenotypically healthy unrelated parents, exhibited ventricular septal defect on clinical and echocardiographic examination. She manifested no severe upper limb abnormality other than bilateral radial deviation of both hands and stiffened elbow articulation (Fig. 2). Her grandfather (Fig. 1; II-3) exhibited severe upper limb defects. Bilateral phocomelia was striking. A rudimentary humerus was noted with three digits attached directly to this rudimentary arm (Fig. 3). The shoulders were narrow and sloping with a decreased range of movement. Physical examination of the heart revealed a widely split and fixed second heart sound and a moderate systolic ejection murmur at the second left intercostal margin. An atrial septal defect was suspected. No echocardiographic evaluation could be performed because of refusal to comply with further investigations. The proband and grandfather both had normal karyotypes. The proband's father (Fig. 1; III-3) had no limb abnormalities. Cardiac evaluation showed no apparent congenital heart defect; however, electrocardiographic examination revealed a first-degree heart block (Fig. 4).

Discussion

A wide variability in expression of the skeletal and cardiac features of HOS has been reported[1-10]. The expression of the skeletal malformations ranges from minor

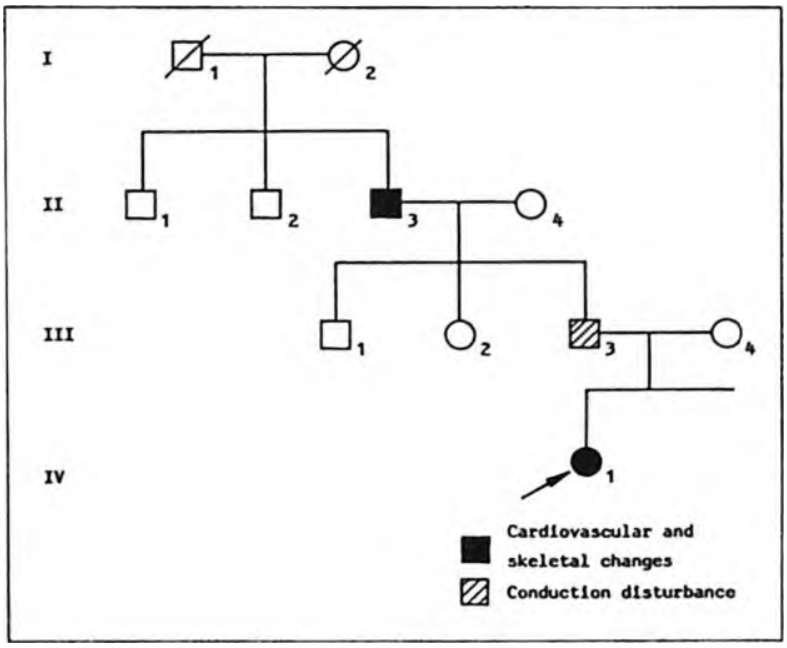

Fig. 1: Family pedigree.

Fig. 2: Proband (granddaughter) (Fig. 1; IV-I).

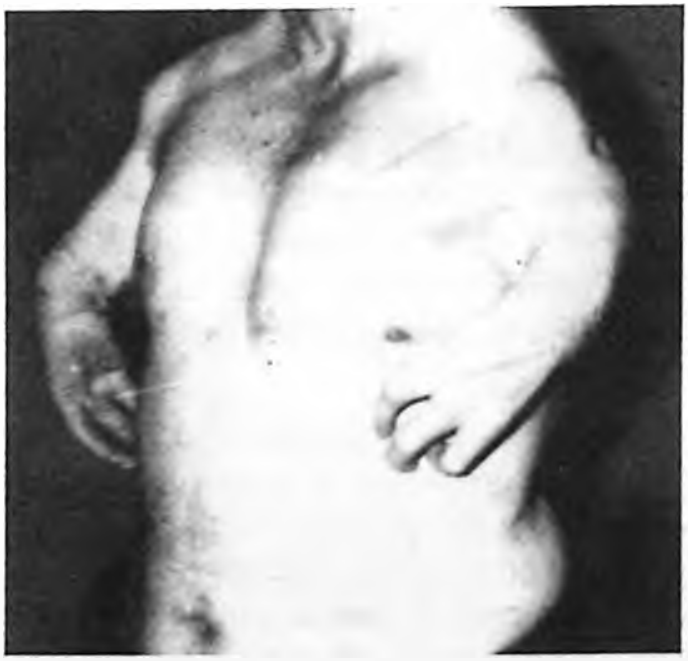

Fig. 3: Grandfather (Fig 1, II-3).

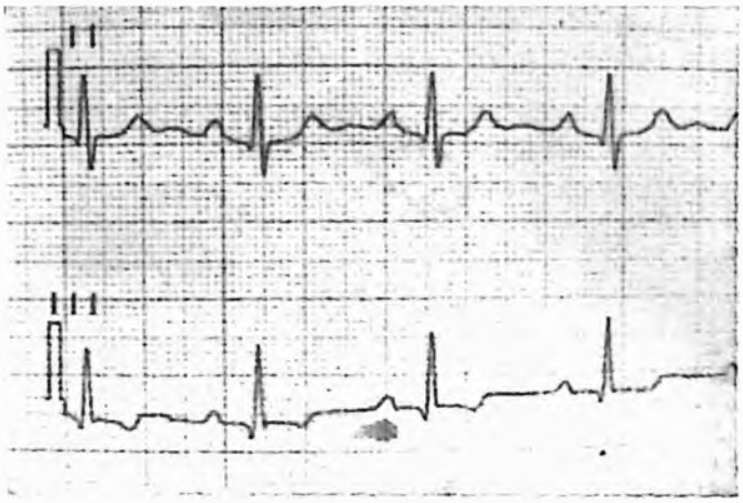

Fig. 4: First degree heart block (father of the proband).

defects, such as limitation of movement of the thumbs, to phocomelia. A range of thumb abnormalities (absent, hypoplastic, or triphalangeal thumb, or partial soft tissue syndactyly of the thumb and index finger) is commonly described. In the analysis of six cases with HOS, Tunçbilek et al.[8] reported bilaterally absent thumb, metacarps and radius. In the most severely affected patients with phocomelia, the humerus is rudimentary or absent with one or two digits attached directly to the trunk. Phocomelia is found in about 10 percent of patients. Çevik et al.[9] reported amelia, a severe skeletal malformation, in an index case and in her father, both with HOS. Other upper limb abnormalities are asymmetric length of arms, limitations of movement at the elbow, hypoplasia of the musculature and narrow and sloping shoulders. The clavicula may be short or broad[1,2,6].

Secundum atrial septal defects are the most common cardiovascular abnormalities; however, ventricular septal defects and conduction abnormalities are also frequently found[1,3,7]. Besides these common cardiac abnormalities, Günal et al.[10] reported common atrium, mitral cleft, mitral insufficiency and pulmonary hypertension in a two-year-old girl in their series of four cases with HOS.

In the presented family variable expression of HOS is well documented (Table I). The grandfather represented a severe form of skeletal abnormality with bilateral phocomelia. Heart defect, on the other hand, was not easy to detect. A careful physical examination revealed moderate systolic ejection murmur. An atrial septal defect was suspected on clinical grounds but could not be confirmed with echocardiographic examination. His son presented no skeletal or cardiac malformation yet conduction abnormality was obvious on electrocardiographic

Table I: Comparison of Clinical Features in Three Affected Members

	Grandfather	Father	Granddaughter
Skeletal changes	severe (phocomelia)	none	mild (radial hand deviation)
Cardiovascular changes	CHD	1° AV block	VSD

CHD congenital heart defect, 1° AV block. first degree atrioventricular block, VSD: ventricular septal defect.

examination. The granddaughter, on the other hand, manifested a muscular ventricular septal defect, with no gross abnormality of the thumbs but minor limitation of their movement and bilateral deviation of the hands. There was no correlation between the severity of the skeletal and cardiac malformations in either affected member.

A gene responsible for HOS (HOS1) has been mapped to chromosome 12 using linkage analysis[11]. Basson et al.[1] recently reported two large families with HOS. Genetic analyses demonstrated linkage of the disease in each family to polymorphic loci on the long arm of chromosome 12[1]. This location has been further refined through the identification of a HOS patient presenting with a complex chromosomal rearrangement involving chromosome 12[12]. Recently, Yi Li et al.[13] showed that TBX5 was mutated in affected individuals in three familial and three sporadic HOS families. The identification of TBX5 as a gene responsible for HOS points out the possibility that members of the TBX family may be responsible for some other inherited developmental disorders.

The proband's father in the presented family manifests no limb or cardiac malformations, only conduction abnormality.

To the best of our knowledge there have been no reports mentioning only conduction abnormality with no associated structural cardiac defects or skeletal abnormalities in HOS. Consequently the present clinical data suggests lack of penetrance in the syndrome with respect to both skeletal and cardiac malformations.

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