Tıp Dergisi
The Medical Journal of Kocatepe
5: 47-53 / Eylül 2004
Afyon Kocatepe Üniversitesi

A Large Kindred With Variable Forms Of Hand and Foot Synpolydactyly

Farklı El ve Ayak Formlarının Bulunduğu Büyük Bir Sinpolidaktili Topluluğu

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ABSTRACT: Of a large synpolydactyly kindred the distinctive phenotypes from each other, homozygous phenotypes produced by the marriages of two heterozygote people and a few minor modifications are presented in this study. The kindred was described in 1995 and has been getting larger since then. We have been visiting the kindred since 2002 May. Evaluating the kindred, we found 125 affected people and described the different phenotypic features clinically and radiologically. Six hand and five foot phenotypes were discriminated. A few distinctive phenotypes undescribed in 1995 were found in the last generation mainly formed by the 89 people born after 1995. Development of different phenotypes may have resulted from incomplete penetrance, variable expressivity, consangineous marriages and multiple genetic factors affecting synpolydactyly inheritance. While the kindred's expansion is a problem in view of public health, it is important surgical standpoint because of different defomities and modified malformations, as well.

Key Words: Synpolydactyly, polysyndactyly, tetrasynpolydactyly

ÖZET: Bu çalışmada geniş bir sinpolidaktili topluluğunun birbirinden farklı fenotipleri, iki heterozigot bireyin evliliklerinden doğan homozigot sinpolidaktili fenotipi ve birkaç minör modifikasyonu sunulmaktadır. Mayıs 2002' den itibaren incelemekte olduğumuz bu topluluk, tanımlandığı 1995 yılından itibaren genişlemektedir. Bu saha çalışması sonucunda 125 sinpolidaktilili birey saptandı ve klinik-radyolojik farklı fenotipik özellikler taşıyan altı değişik el ve beş farklı ayak deformitesi grubu tanımlandı. Son jenerasyonu oluşturan ve 1995'ten sonra doğan 89 çocuk arasında daha önceki çalışmada tanımlanmamış klinik bulgu açısından birkaç farklı özellik belirlendi. Fenotiplerdeki farklılık sinpolidaktili kalıtımında etkili olan düşük penetrans, ekspressivite çeşitliliği, yakın akraba evliliği ve çoklu genetik faktörler nedeniyle gelişmiş olabilir. Topluluğun genişlemesi halk sağlığı açısından bir sorun teşkil ederken, değişik deformitelerin ortaya çıkması da cerrahi teknik açısından önemlidir.

Anahtar Kelimeler: Sinpolidaktili, polisindaktili, tetrasinpolidaktili.

INTRODUCTION

Synpolydactyly (SPD) is a rare, dominantly inherited limb malformation that typically consists of ¾ syndactyly in the hands and 4/5 syndactyly in the feet, with digit duplication in the syndactylous web. Incomplete penetrance and variable expressivity both between and within affected families are common. SPD is the first human malformation syndrome, shown to be caused by mutations in a HOX gene, HOXD13 (3,6). As for polydactyly (PD) and syndactyly (SD), they are the most frequent anomalies, often associated with each other, affecting several family members (12,15). Just as these anomalies can be sporadic, as do they occur along with some skeletal or extraskeletal abnormalities (1). While PD is characterized by supernumerary digits on the hands and/or feet, SD is characterized with webbed and/or fused fingers (5). SPD and polysyndactyly (PSD) are the complicated entities consisting of SD and PD along with each other. While SD is conspicuous component in SPD, PD is so in PSD.

Five types SD have been differentiated so far. One of them, SPD, is SD type II. SPD consists of hidden central polydactyly between the middle and ring fingers (3). PD is usually classified into three major groups based on ray involvement: **1.**Preaxial (Medial ray) **2.**Central (Central rays, 2nd, 3rd, 4th) **3.**Postaxial (Lateral ray) (16). Postaxial PD is the

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most common congenital malformation of the forefoot (9,10,16). Venn-Watson's (15) and Phelps's (11) series are the largest PD series to have been reported so far. Reviewing the ray involved and precise morphologic patterns, Watanabe et al classified the PD of foot (16).

We present here the recent findings of the very large and interesting SPD kindred described in 1995 (12). The kindred has been enlarging and developping different phenotypes since then. As these differences are more common in the 89 people born after 1995, possible minor genetical modifications can be considered

MATERIAL AND METHODS

The kindred have been evaluated by our physician team including the authors. The kindred was described first by Sayli et al in 1995 (14). Akarsu et al were the first authors to submit the 7 homozygote synpolydactylized offsprings' phenotypic features (2). Since 2002 May, we have been visiting the villages where the kindred has been inhabiting for the last 160 years. Affected and unaffected subjects were interviewed and pedigrees of the last five generations were constructed. Information about dead person was obtained from their living relatives. The affected individuals were asked to attend to clinic for further diagnostic studies and recontsructive surgical procedures. The radiological and clinical findings were reviewed for morphologic analysis. The full skeletal and extraskeletal examinations were performed to diagnose any additional abnormality or any syndrome and to determine whether the surgical procedures could improve the hand function and could solve the foot problems. Evaluating retrospectively the records of the population from the kindred, we submit the phenotypic features of the 125 people including 89 new individuals born after 1995.

RESULTS

The 125 people from the recent three generations were seen during the field investigation and recorded as "affected people". The approximate population of the kindred over the last five generations was 245. The 89 out of 125 were born after 1995. While the population of village where the kindred was mainly concentrated was 1024 in 1992, it is 1800 now. The kindred has been getting larger gradually since 1995. The last generation was made up mainly by the people born after 1995. Forty four people attended to the clinic and were examined clinically and radiologically. A total of 71 surgical procedures were performed on foot and/or hand problems of 27 people so far. The average age of the operated patients was 6,3 years. Except the 22, people had the deformity in their all extremities (Tetrasynpolydactyly). There were no associated extraskeletal anomalies except that two boys with homozygote pattern had hypospadias. There was no sex related differences in phenotypes.

Clinical and radiologic findings

With respect to hand anomalies, we were able to discriminate six different phenotypes: I).Typical SPD (SD type II) (88-69%) II).Incomplete SD with index hypoplasia (2-2%) III).Central PD of long finger with clinodactyly of thumb (12-10%) IV).Triple SPD (Ulnar three rays) (10-8%) V).Postaxial PD with clinodactyly of little finger (1-1%) VI).Homozygote phenotype (12-10%).

From the point of foot, there were five different phenotypes: I).Normal feet (22-18%) II).Fifth ray metatarsal duplication (88-68%) III).Crossed PD (1-1%) IV).Fifth ray middle phalangeal duplication (2-2%) V).Homozygote phenotype (12-10%).

The adults were used to living together with their hand deformities, so they did not want surgery. The children with hand deformities had function loss in variable rates in connection with the phenotypes and age. As well as the severe function loss, homozygotes' hand were considerably hypoplastic. In virtually all individuals with anomaly had some problems with wearing shoes. The main problem in this group was painful callosities formed by shoes.

Typical SPD

Named SD type II, classical SPD was the largest hand phenotype. It was characterized by the presence of bilateral 3/4 SD with partial fourth finger duplication in the syndactylous web. Mainly in the olders, joint contractures were so severe that there were no passive motion in the involved joints. In some patients the syndactylized phalanges were delta shape (Fig. 1).

Foot phenotypes were variable. While 22 people were found to have normal feet, most people had fifth ray metatarsal PD. This type presented complete fifth ray duplication with hypolastic metatarsal which had no articulation with tarsal bone. In virtually all of them, duplicated fifth toe was also hypoplastic. There was a severe synonychia. Since the real fifth toe was diverged from longitudinal axis, the patients had painful callosities because of shoe wearing (Fig. 2). One patient with

typical SPD had "crossed polydactyly", which is described as the combination of preaxial PD of foot with the postaxial or central PD of hands (7). The duplicated great toe consisted of kissing-delta phalanx (8,17). He had fifth ray metatarsal duplication in his other foot (Fig. 3).

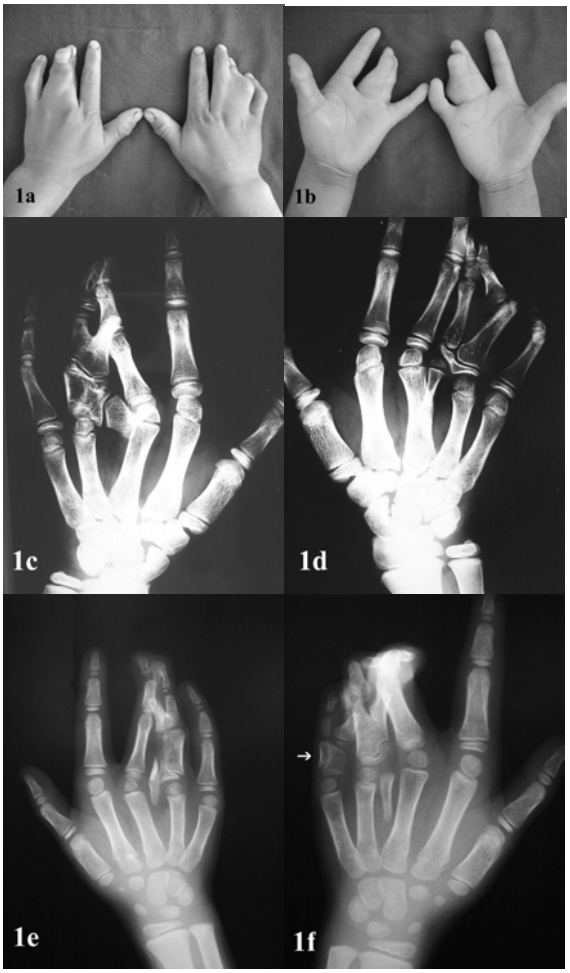

Figure 1: Typical SPD. **a).**Dorsal appearance. **b).**Palmar sides. **c).**X-ray of left hand, complex fusion between the bones. **d).**X-ray of right hand, clino-camptodactyly of fourth finger. **e).** Note the delta-shaped epiphysis in duplicated proximal phalanges. **f).** Delta phalanx (arrow).

Incomplete SD with index hypoplasia

Two people were found to have this phenotype. They had incomplete unilateral syndactyly in the second web. One of them had congenital distal part agenesis in her ulnarly deviated index. She had no anomaly in her feet, but the other had fifth ray metatarsal duplication (Fig. 4).

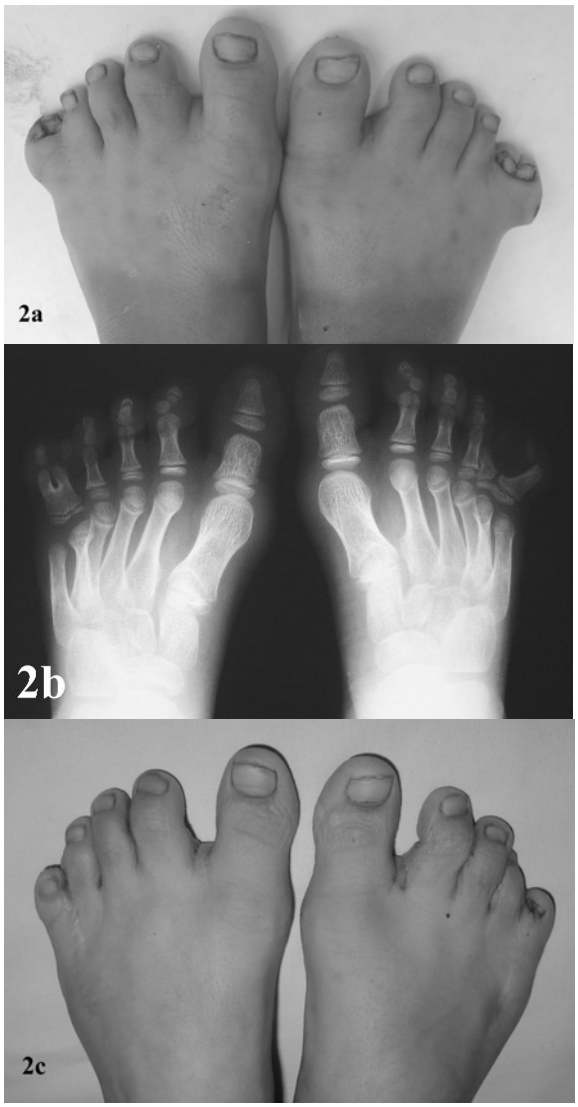

Figure 2: The largest phenotype: fifth ray metatarsal duplication. **a).** Divergence of the most lateral toe. **b).**The hypoplastic duplicated metatarsals have no articulation with tarsal. The distal parts of fifth and sixth rays are fused. **c).** After resection of fifth ray, the patient relieved the callostasis problems.

Central PD with thumb clinodactyly

Central PD was in the third ray. These patients had also camptodactyly of little fingers and clinodactyly of thumbs because of delta phalanx (4,8). Like most people, they had also fifth ray metatarsal duplication. They had no function loss and complaints with their hands except cosmetic appearance. However they had a lot of problem with wearing shoes (Fig. 5).

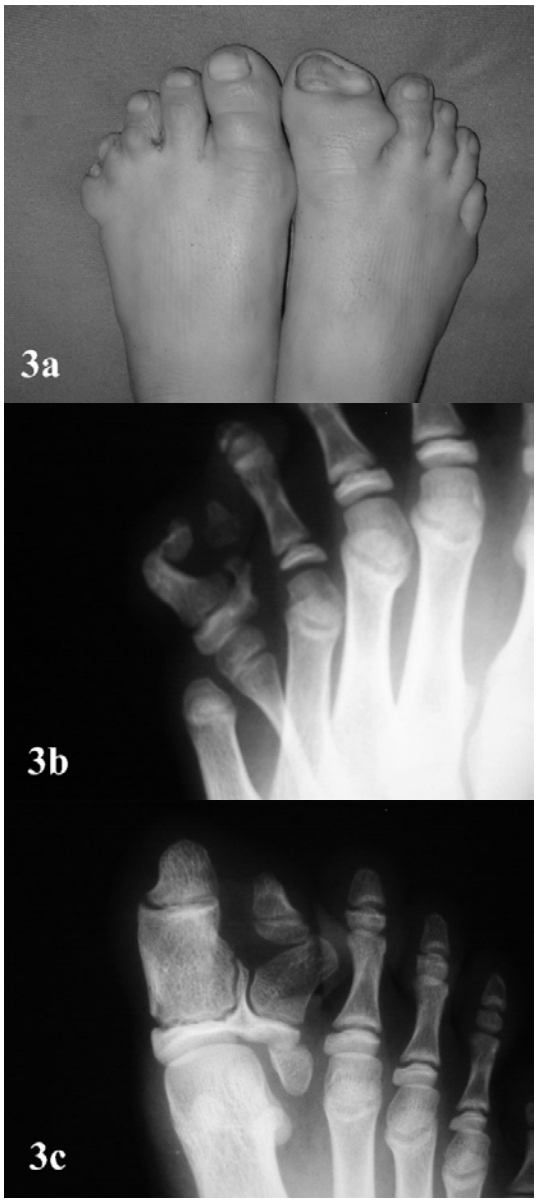

Figure 3. The feet of the patient xith crossed PD. **a).**Preaxial duplication on rigth, postaxial duplication on left. **b).** Fifth ray duplication of the hypoplastic metatarsal with duplicated phalanges and the absence of phalanges of real fifth ray. **c).**Preaxial duplication of great toe with incomplete kissing-delta phalanx with united epiphysis.

Triple SPD

In the patients with triple SPD, little finger was also involved in the syndactylized mass. They had also fifth ray metatarsal duplication. Function loss and deformity of proximal interphalangeal joint (PIP) were more severe than that of the hands with typical SPD (Fig. 6).

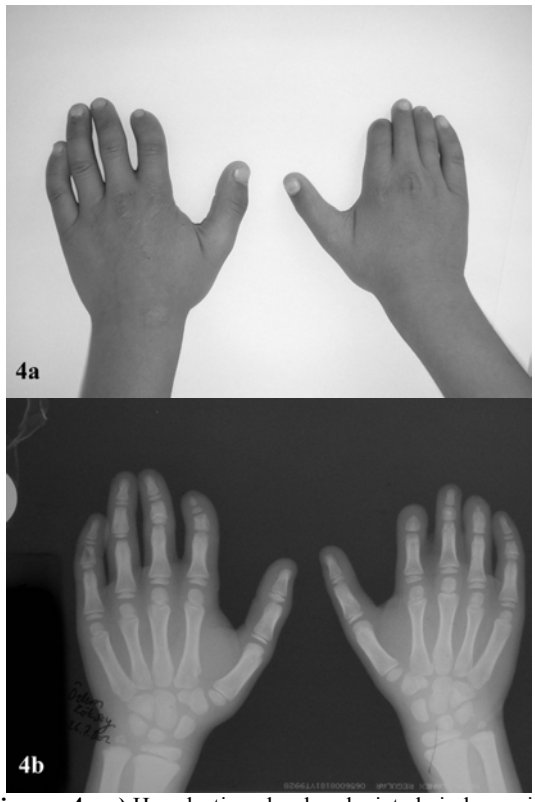

Figure 4. a). Hypolastic ulnarly deviated index with incomplete SD on left. **b).** Radiographs show agenesis of distal parts of right index. The middle phalanx of left index is in delta shaped causing ulnar deviation. Hypoplasia and cone epiphysis in the middle phalanges are also seen. There is a marked hypoplasia in the right fourth finger with a small ossicle as distal phalanx.

Postaxial PD with clinodactyly of little finger

One person with this distinctive phenotype was found to have clinodactyly deformity of little finger along with metacarpophalengeal joint (MP) incomplete duplication as well as a different type PD in his feet. He had fifth ray middle phalangeal duplication in one side. The deformity of the other side was similar with the patient with crossed PD (Fig.3b). Rudimentary fifth ray metatarsal was articulated with the fused proximal phalanges (Fig. 7).

Homozygotes

They had four affected extremities. There were 12 people with homozygote genetical pattern from seven marriages between two heterozygote parents. Their foot and hand anomaly was very different from that of their parents. Since the most obvious appearance was severe hypoplasia in hands, such as paw-like appearance, we called the deformity "hypoplastic synpolydactyly" (HSPD). The ulnar part of hand was made up by severely hypoplastic hy-

pothenar muscles and ulnarly drifted ulnar half of hand. The clinodactilized index had incomplete SD with neighboring long finger. Thumbs and thenar region were also hypoplastic. There were duplicated thumbs in some patients. The palmar side appeared to be fatty. There was so severe function loss that the patients could make a little grasping by only flexing the MP joints. Radiology of the hands showed markedly underdevelopped, unshaped, hypoplastic metacarpals, carpals and phalanges. In general bone age was not appropriate with calendar age. Some abnormally shaped phalanges were observed to have had two growth plates at its both ends, we called them "biepiphyseal phalanx". The distal parts of fingers were rudimentary to the extent that phalanges could not be identified clearly. Index fingers appeared to be seperated from the others because of evident clinodactyly. Carpal bones were distinctly atypical in shape, and more than the normal number in some older children. They seemed to be scattered rather than being in their normal position.

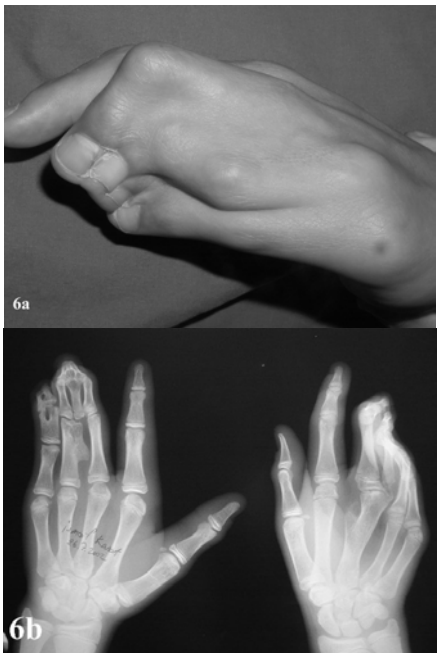

Figure 6. Triple SPD. **a).** Note the little finger involved in the synpolydactylized mass. **b).** Anteroposterior radiographs.

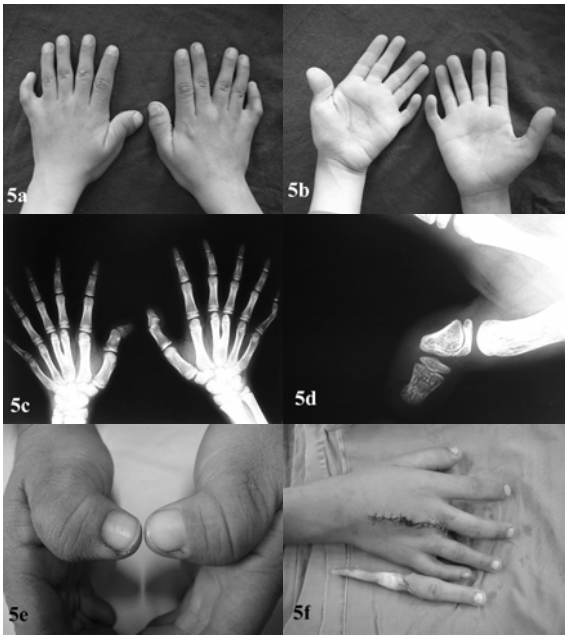

Figure 5: Central polydactyly with thumb clinodactyly. **a).**Dorsal view. **b).**Palmar view. It is difficult to discriminate the duplicated finger. **c).**Radiographs show the splitting of third metacarpals without evidence of distal SD. Note the clinodactyly of the right thumb and camptodactyly of both little fingers. **d).** Severe clinodactyly in thumb because of delta phalanx. **e).**Thumbs are bilaterally clinodactylized in some patients. Note the cone epiphysis in the distal phalanx. **f).** After resection

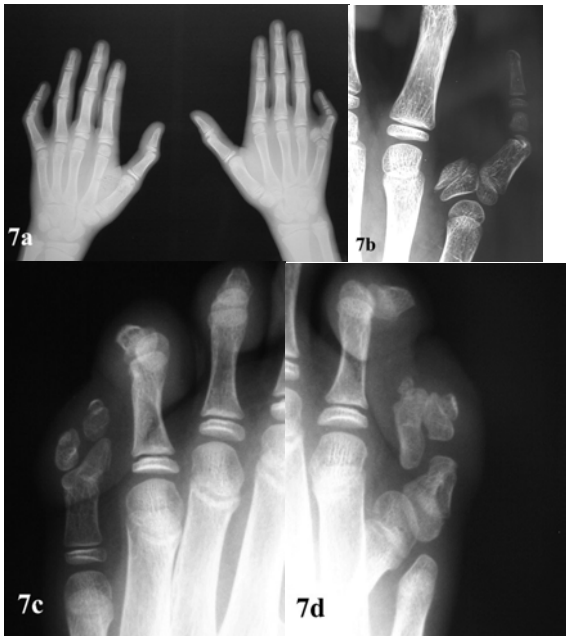

Figure 7: Postaxial PD of hands and feet. **a).**Radiograph shows clinodactyly of both little finger with incomplete MP duplication of fifth ray. **b).** The apperance of duplicated part in details. Note the epiphyseal longitudinal bracket associated with proximal delta phalanx and markedly hypolastic middle phalanx. **c).**Middle phalangeal duplication in left foot. Note the fusion of PIP joint. **d).** Radiology of right forefoot. Fifth ray duplication of the hypolastic metatarsal like the case in figure 3b.

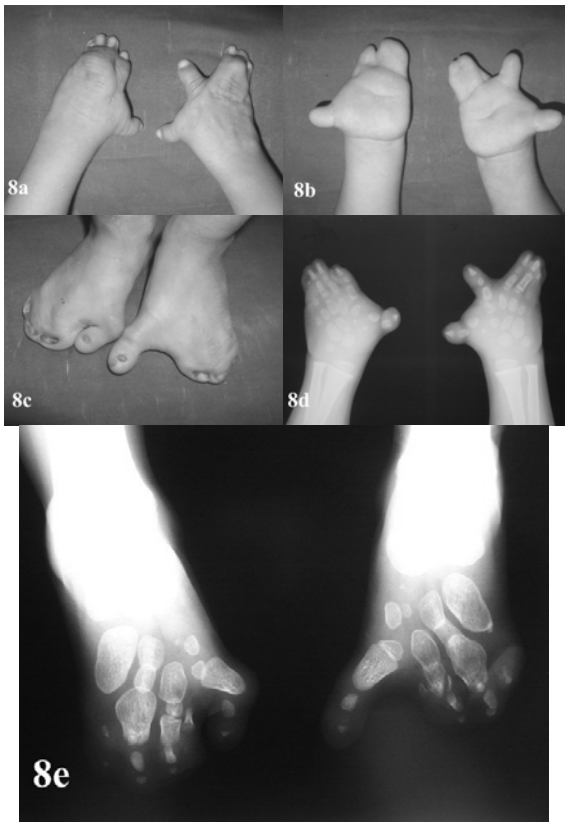

Figure 8. Homozygote phenotype. **a).**Dorsal appearance of both hands. **b).**Palmar side. Paw-like apperance. **c).**Clinical apperance of both feet. **d).** Bizare hands with marked undevelopped, unshaped and hypolastic bones. Note the biepiphyseal phalanx on the right side and broadened metacarpals associated with undertubulation. **e).**Undifferentiation of foot bones is obvious.

Mostly, great toes were prominent bilaterally and the first web space was very enlarged. The halluces were considerably greater than toes. The toes were within the syndactylized mass. The nails of the toes were far dysmorphic. Radiologically, talus, calcaneus and navicular were normal. There were large bony islands resulting from fusions of cuneiforms and metatarsals and severe dismorphism. There appeared to have been block metatarsals and tarsals. It was clear that both of second metatarsal bones were absent. All the metatarsal bones were short, broad and fused. Differentiation between metatarsal bones and proximal phalanges were not clear in some. Just as they had a lot of problem with wearing shoes because of excessivelly flourished and angulated great toe, so too had they difficulties because of SPD. A great number of callosities and palmarly diverged extra toe was interfering with the patients' walking (Fig. 8).

DISCUSSION

As stated by Sayli et al (14), the kindred presented here appears to be the largest one ever reported. Just as it has been enlarging so far, so will it grow as of now. As far as an autosomal dominant deformity is concerned, it is very difficult to lessen the rate of offsprings with deformity. For instance, birth of new 89 subjects after 1995 caused the size of kindred to increase, developing the last generation. Acknowledging the high possibility of affected offsprings birth, affected people, even two affected people, have been getting married. Marriages between two affected people have been only in the second and third generation, producing the homozygote offsprings.

SPD is always inherited as an autosomal dominant disorder, showing reduced penetrance, variable expressivity and no sex related difference (2,5). As a result of this, even two affected parents can have normal offsprings like some families in this kindred. Continuously increasing the size of family and kindred tree, affected parents have been causing the birth of new affected subjects until they have normal child. Consequently, the economic and psychosocial problems for both parents and children have been getting more and more complicated. It is obvious that the homozygote people will be certain to own affected offsprings in the next generations.

We could not observe foot malformation without hand deformity. But the 22 people with hand deformity had no foot anomaly. Except homozygotes, the common foot anomaly was fifth ray metatarsal duplication regardless of hand phenotype. Only three heterozygote people had different foot phenotype which were preaxial PD and fifth ray middle phalangeal duplication.

There are a few different classification systems based on foot anomaly. While some authors use morphologic findings, the others use clinical appearance. Radiologic analysis revealed that radiologic appearances can be different even if the clinical appearances were similar. Therefore classification and differential diagnosis should be made radiologically (16). Whichever classification system is used, homozygous phenotype should be involved in SPD subgroups.

We found four adult people operated previously. They had had total resection of lateral two rays of their feet. Although recommended in the literature, in the treatment of postaxial polydactyly, the excision of the most lateral toe is not always correct. The duplicated digit or the digit seeming to

be aberrant should be excised. Therefore, in view of that it describes the duplicated part, the classification system used by Watanebe et al is more beneficial for determining the which part to be removed. Contrary to the problems with hand deformity, the patients preferred to be operated only after their foot problems had become symptomatic. In defiance of the secondary foot problem, PD of the foot should be treated before the walking age is reached. Thus, maximal time will be given to the patient to fit into shoes and to remodel (15). The more important than removing the extra-digits is solving the secondary problems of foot. Namely, despite removal of the extra digits, remaining deformities may constitute a major disability (15).

Unless the surgery of the hand had not been performed before the development of fixed joint contractures and malalignments of bones, it could not be so effective as to improve the whole hand function. The surgery performed in early childhood is restoration of whole hand and its function rather than only removing the extra bones or seperating the syndactylized fingers.

In conclusion, a number of important genes and some modifiers take a role in the etiology of synpolydactyly. Because of these modifiers and multiple factors, the phenotypic features of the kindred have been altering gradually. As in our series, homozygote phenotype, postaxial incomplete polydactyly with clinodactyly and central polydactyly with thumb clinodactyly are the different phenotypic features. Although the patients analyzed in this study carried the same +9 additional Alanine residues, finding of different phenotypes points the action of other genetic factors. Additional investigations are required to reveal these modifiers or the reason of phenotypic differences.

ACKNOWLEDGEMENTS

We are thankful to Dr. Mehmet Eray Bozan for his contributions in this study. Despite his death (November 16, 2004), we will benefit from his studies in future as well.

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