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# Genetic study of congenital limb anomalies among Egyptian children

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## ABSTRACT

**Objective:** This study has been conducted to reveal genetically-determined factors that underlie the development of congenital limb anomalies among a sample of Egyptian infants and children. These data might prove useful in taking preventive measures and/or providing proper counseling to concerned families.

**Subjects and Methods:** The study comprised studying 140 (One hundred and forty) Egyptian children with congenital limb anomalies. They consisted of (98) males and (42) females ranging in age from 10 days to 18 years. All cases were selected from among patients attending the outpatient medical genetics clinic, faculty of medicine, Ain-Shams university, Cairo-Egypt. Enrolled cases were subjected to a list of investigations including complete history with pedigree construction, anthropometric measurements and full clinical examination. In addition, specific radio-imaging studies and laboratory investigations were done for cases necessitating further diagnostic workup.

**Results:** The results of the study revealed that isolated limb anomalies were found in (55) patients representing (39.3%) of cases. The remaining eighty five (85) patients constituting (60.7%) of enrolled cases comprised two groups: those with limb defects as part of a well defined genetic syndrome (Syndromic limb defects) (76 patients - 54.3%) and those with limb defects as part of a chromosomal aberration syndrome (9 patients - 6.4%). Genealogical data of the study revealed that parental consanguinity is found in (47.3%) of cases with isolated limb defects, in (72.3%) of cases with syndromic limb defects and in (44.4%) of cases with limb defects due to chromosomal abnormalities.

Valid history of prenatal drug intake by the mother was found in (43.6%) of cases with isolated limb defects, in (25%) of syndromic limb defects and in none of the cases with chromosomal abnormalities.

**Conclusions:** Detailed analysis of data of the study drew useful recommendations regarding many aspects like the possibility of prenatal diagnosis of most cases as well as the availability of many curative and/or palliative intervention measures for early detected and managed cases. Of prime importance, however, is the urgent need of alerting gynecologists and obstetricians taking care of pregnant women to the important role played by iatrogenic prescription of drugs during pregnancy in causation of many types of congenital limb anomalies. Cessation of this non-based evidence medical attitude is necessary and can result in a significant reduction in drug-induced congenital limb anomalies among newborns.

**Key Words:**

Limb anomalies, Egyptian children, consanguinity, chromosomal abnormalities.

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## INTRODUCTION

Limb malformations, like most other human malformations, can be categorized into three major groups: a genetically-determined group comprising anomalies representing a part of the pathogenetic spectrum of many single gene and chromosomal disorders, an environmentally-induced group embracing limb malformations caused solely by the teratogenic effects of some drugs and a multifactorial group encompassing anomalies due to the combined interactions of an environmental teratogen and a susceptible genetic background.

Environmental factors implicated in congenital limb defects (CLD) comprise many and various teratogens, the best known of which is thalidomide which causes a wide spectrum of severe limb defects involving both the upper and the lower limbs via many molecular pathogenetic mechanisms[1]. Other teratogenic drugs include dilantin, phenobarbitone, aminopterin, chlorambucil, nitrogen mustard and most chemotherapeutic and immunosuupressive agents. Other drugs that might also induce limb anomalies include vitamin A in large doses and many antibiotics like tetracyclines and penicillins.[2] In addition to, other teratogenic agents capable of inducing limb anomalies in developing fetuses include physical teratogens like excessive exposure to X ray or to irradiation and physical teratogens like the rubella virus which causes many limb defects in newborns affected with the congenital rubella syndrome.

The susceptibility to, as well as the spectrum and severity of, congenital limb defects depend on many complicated interactions between implicated and causative factors including the nature of the permissive genetic background, the dose and timing of exposure to the teratogenic agent(s) and the integrity of the intrauterine environment. Local uterine and pregnancy-related factors are well known causes of congenital limb anomalies of non-genetic etiology. Instances of limb reduction defects are reported with a presumed common underlying etiologic theme of early in utero limb compression, deduced as being due to a bicornuate uterus in four instances, a large fibroid in one instance and early amnion rupture with transient amniotic fluid loss in two instances. Similar types of limb reduction defects have been experimentally produced as a consequence of early withdrawal of amniotic fluid with resultant compression of the developing limbs, leading to vascular disruption. A similar mechanism is hypothesized to have caused these instances of limb reduction defects.[3]

There are many approaches to classify CLD. The Clinical classification design based on the phenotype of the defect(s) suggested by Swanson[4] still holds useful in practice. This design classifies limb malformations into seven pathological-phenotypic categories according to the type,extent, shape and underlying etiologiacal factors implicated in their causation. However, many discrepancies

were found upon comparing data from many other studies using the same classification parameters. One explanation for these discrepancies is a lack of uniformity in the classification of Swanson which may be caused by out-dated knowledge of the pathogenesis of congenital limb anomalies. Therefore, it seems necessary to describe the anomalies instead of the diagnoses. A new descriptive method for all anomalies of the upper limb based on this approach has been evaluated and might prove more practical than that delineated by Swanson.[5]

Prenatal diagnosis of most CLD is possible via safe fetal imaging with ultrasound. Newly improved techniques like 3 Dimensional and 4 Dimensional fetal ultrasound imaging allow proper and precise diagnosis, thus allowing for early postnatal management procedures to be implemented. Intrauterine surgical intervention might also be tried for some preventable defects, eg. Developing amniotic fluid bands.[6]

## SUBJECTS

The present study comprised 140 (One hundred and forty) Egyptian children with congenital limb anomalies. They consisted of (98) males and (42) females ranging in age from 10 days to 18 years. All cases were selected from among patients attending the outpatient Medical Genetics clinic, faculty of medicine, Ain-Shams university, Cairo-Egypt over a time period of seventeen months starting November 2007 through April 2009.

## METHODS

Enrolled cases were subjected to a list of investigations including complete prenatal, personal and family histories with pedigree construction, full clinical examination with special emphasis on anthropometric measurements and the presenting limb defect(s). Radiological assessment of apparent and possibly hidden, bone anomalies was performed to all cases. In addition, specific supplementary and confirmatory diagnostic investigations were conducted according to the provisional diagnostic categorization of the concerned patients. These procedures included abdominopelvic ultrasonography, echocardiography, cytogenetic studies for suspected chromosomal aberrations and biochemical investigations for cases with suspected metabolic/hormonal underlying etiology.

## RESULTS

The results of the present work (Table 1) revealed the following findings:

1. Isolated limb anomalies were found in (55) patients representing (39.3%) of cases. The remaining eighty five (85) patients constituting (60.7%) of enrolled cases comprised two groups: those with limb defect(s) as part of a well defined genetic syndrome (syndromic limb defects) (76 patients - 54.3%) and those with limb defects as part of a chromosomal aberration (9 patients - 6.4%).

2. Genealogical data of the study revealed that parental consanguinity is found in (47.3%) of cases with isolated limb defects, in (72.3%) of cases with syndromic limb defects and in (44.4%) of cases with limb defects due to chromosomal abnormalities.

**Table 1:** Clinical and genealogical data of cases with congenital limb anomalies:

| Etiological Category | Syndromic Limb Defects | Limb Defects Due To Chromosomal Aberrations | Isolated Limb Defects |
|---|---|---|---|
| Number of cases | (76 Patients - 54.3 %) | (9 Patients - 6.4 %) | (55 Patients - 39.3 %) |
| Sex | Males : 49 cases<br>Females : 27 cases | Males : 6 cases<br>Females : 3 cases | Males : 43 cases<br>Females : 12 cases |
| Age | One month – 27 years | One day – 15 years | 10 days – 17 years |
| Parental Consanguinity | 72.3 % | 44.4 % | 47.3 % |
| Family History | Similar anomalies : 4 cases<br>Other limb anomalies : 1 case | Similar anomalies : 1 case | ---------- |
| History Of Drug Intake During Pregnancy | In 25 % of cases | ---------- | In 43.6 % of cases |
| Observed Limb Anomalies | Absence defects : 11 cases<br>Polydactyly: 23 cases<br>Hypertrophy: 10 cases<br>Contractures: 10 cases<br>Syndactyly: 4 cases<br>Brachydactyly : 10 cases<br>Hypoplasia: 5 cases<br>Arachnodactyly: 3 cases | Polydactyly : 3 cases<br>Syndactyly : 2 cases<br>Contractures : 1 case<br>Absence defects : 1 case<br>Brachydactyly : 1 case<br>Arachnodactyly : 1 case | Absence defects : 24 cases<br>Polydactyly : 14 cases<br>Hypertrophy : 5 cases<br>Contractures : 7 cases<br>Syndactyly : 4 cases<br>Brachydactyly : 1 case |
| Associated Syndromes / Aberrations | Achondroplasia<br>Apert Sydrome<br>Carpenter Sydrome<br>Coffin Lowry Sydrome<br>Diastrophic Dysplasia Sydrome<br>E.E.C. syndrome<br>Epidermolysis Bullosa<br>Fanconi syndrome<br>Focal Dermal Hypoplasia<br>Goldenhar syndrome<br>Hand-Foot-genital syndrome<br>Hanhart syndrome<br>Holt-Oram syndrome<br>Klipple-Feil Sydrome<br>Laurence Moon Sydrome<br>Marfan syndrome<br>Meckel Sydrome<br>Neurofibromatosis type I | Turner syndrome<br>Down syndrome<br>5p- syndrome<br>18q- syndrome<br>Mosaic 22q- syndrome<br>10q+ syndrome | ---------- |

3. Valid history of prenatal drug intake by the mother during the first trimester was found in (43.6%) of cases with isolated limb defects, in (25%) of syndromic limb defects and in none of the cases with chromosomal abnormalities. In order of frequency, the list of these drugs included antibiotics, non-steroidal anti-anflammatory drugs, Progesterone hormonal preparations and systemic antifungal drugs.

4. Whereas specific defects compatible with the known phenotypes of the underlying diseases were the rule for cases with syndromic and chromosomal etiologies, predilection of specific phenotypes characterised by deficient growth was detected in all cases with isolated limb defects with a positive history of prenatal drug intake by the mother. These deficient growth patterns were expressed clinically

as absence limb anomalies including acheiria, apodia, ectrodactyly, aphalangia, transverse hemimelia and single absence of the radius and the ulna with consequent deformity of affected limbs.

**Table 2:** List of photos of some cases of the study with congenital limb defects:

| SN | Disorder / Aberration / Etiology | Description of The limb anomaly |
|---|---|---|
| 1 | Laurence Moon Syndrome | Bilaterally fully develoed postaxial polydactyly of both hands and feet. |
| 2 | Klipple Feil syndrome | Plain X-ray showing right preaxial polysyndactyly of the right foot |
| 3 | Robinow syndrome | Bilateral forearm mesomelia and brachydactyly |
| 4 | Teratogenic exposure in-utero | Acheiria of left upper limb |
| 5 | Teratogenic exposure in-utero | Left sided apodia, absent fibula and short tibia |
| 6 | Teratogenic exposure in-utero | Teratogenic Bilateral split hand and ectrodactyly |
| 7 | Teratogenic exposure in-utero | Bilateral acheiria, left sided apodia and ectrodactyly of right feet |
| 8 | Isolated multiple limb anomalies | Monodactyly of right hand and macrodactyly and split left hand |
| 9 | Holt-Oram syndrome | Right humero-radial synostosis, absent 1$^{st}$ metacarpal and absent 2$^{nd}$ phalanx of right thumb |
| 10 | Goldenhar syndrome | Absence of right radius and right thumb |
| 11 | Hanhart syndrome | Right acheiria and left apodia |
| 12 | Fanconi pancytopenia syndrome | Bilateral bifid thumbs |
| 13 | Isolated limb anomaly | Macrodactyly of left 2$^{nd}$ toe |
| 14 | Oro-Facio-Digital syndrome | Extra transverse metatarsal and polysyndactyly of right 2$^{nd}$ toe |
| 15 | E.E.C. syndrome (Ectrodactyly-Ectodermal dysplasia-Clefting syndrome) | Bilateral splitting and ectrodactyly of both hands and feet |
| 16 | Isolated limb anomaly | Teratogenic hand-like-foot anomaly (Ambroise Pare like malformation) |
| 17 | Isolated limb anomaly | Teratogenic caudal regression syndrome |
| 15 | Isolated limb anomaly | Teratogenic bilateral split hand deformity |
| 19 | Hand-Heart syndrome type I | Monodactyly of lt. hand and ectrodactyly of rt. hand |

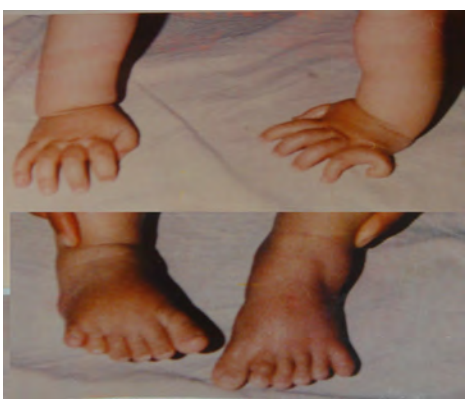

**Fig. 1:** Laurence Moon syndrome.

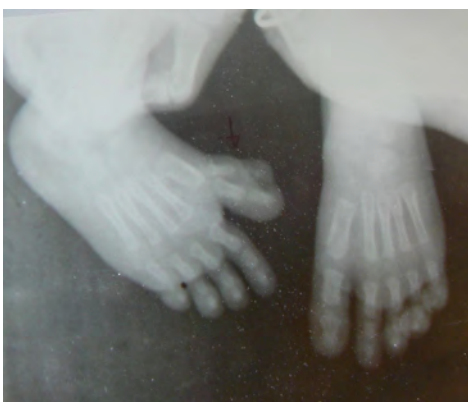

**Fig. 2:** Klipple Feil syndrome.

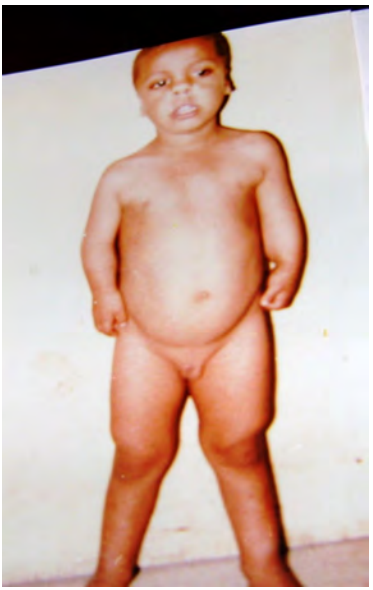

**Fig. 3:** Robinow syndrome.

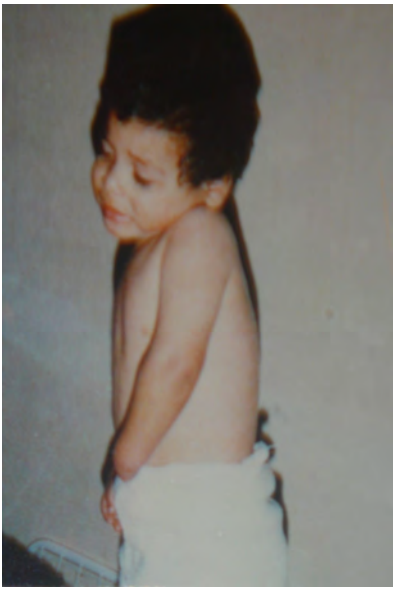

**Fig. 4:** Teratogenic Acheiria of left upper limb.

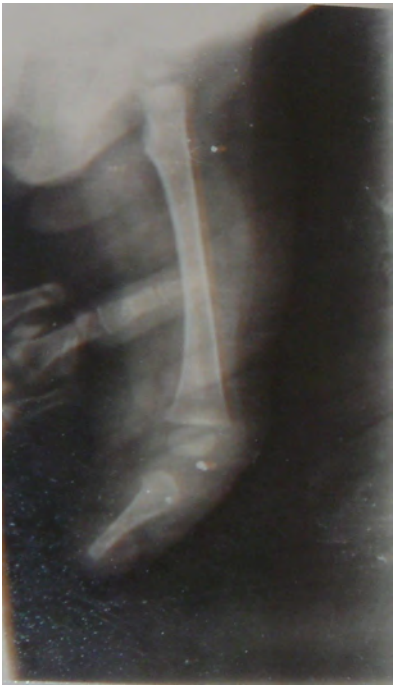

**Fig. 5:** Teratogenic left sided apodia, absent fibula and short tibia.

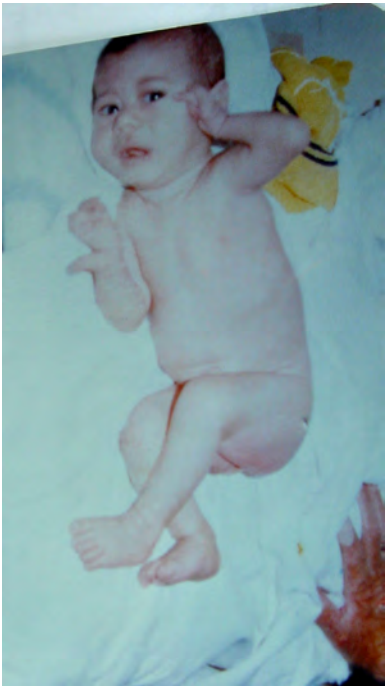

**Fig. 6:** Teratogenic bilateral split hand deformity.

**Fig. 7:** Teratogenic Bilateral acheiria, left sided apodia and ectrodactyly of right feet.

**Fig. 8:** Monodactyly of right hand and macrodactyly and split left hand.

**Fig. 9:** Right humero-radial synostosis In Holt-Oram syndrome.

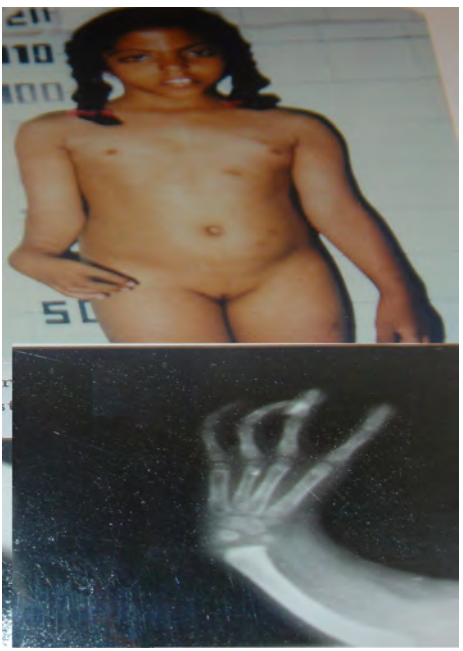

**Fig. 10:** Absence of rt. Radius and rt. thumb in Goldenhar syndrome.

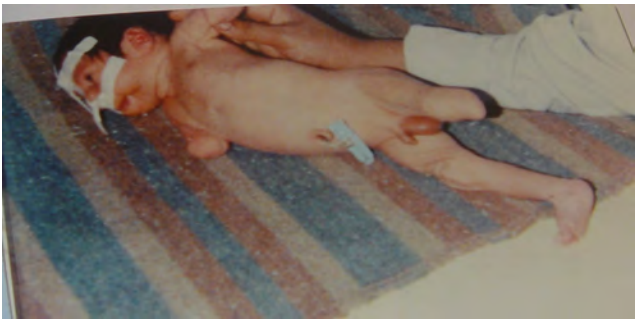

**Fig. 11:** Right acheiria and left apodia in Hanhart syndrome.

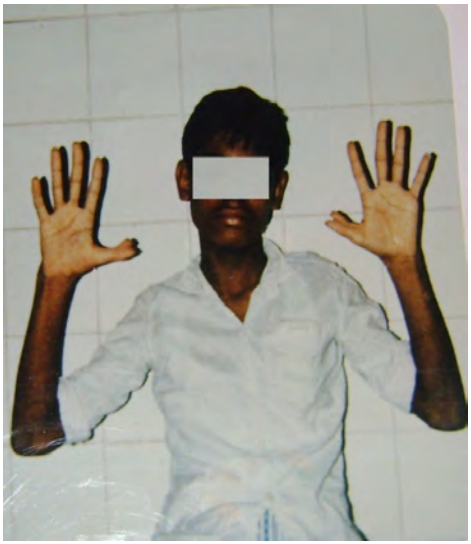

**Fig. 12:** Bilateral bifid thumbs in Fanconi syndrome.

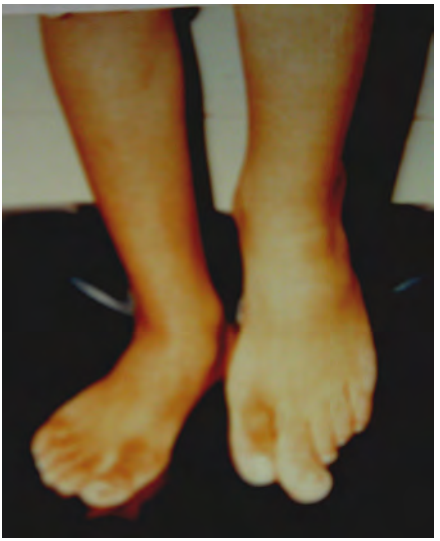

**Fig. 13:** Macrodactyly of left 2nd toe.

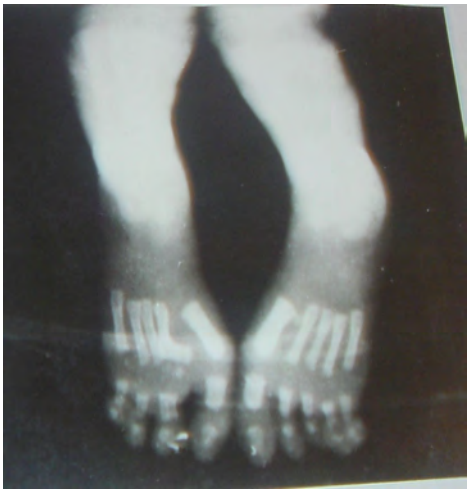

**Fig. 14:** Extra transverse metatarsal and polysyndactyly of right 2nd toe in OFD syndrome.

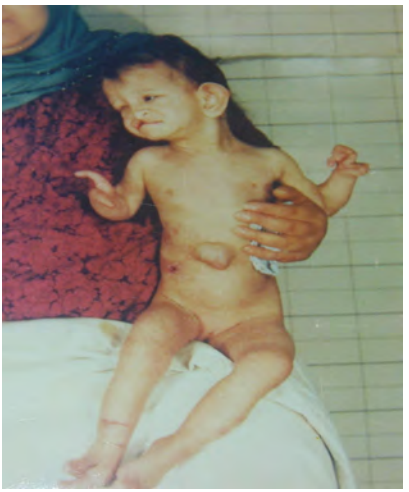

**Fig. 15:** E.E.C. syndrome.

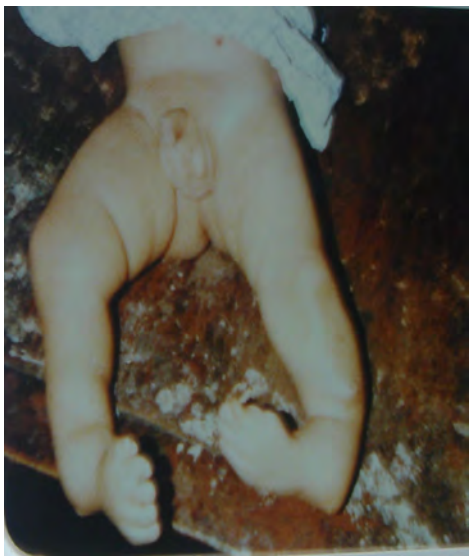

**Fig. 16:** Teratogenic hand-like-foot anomaly (Ambroise Pare like malformation).

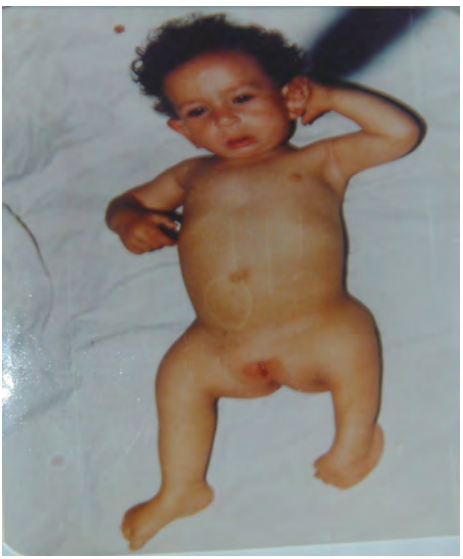

**Fig. 17:** Teratogenic caudal regression syndrome.

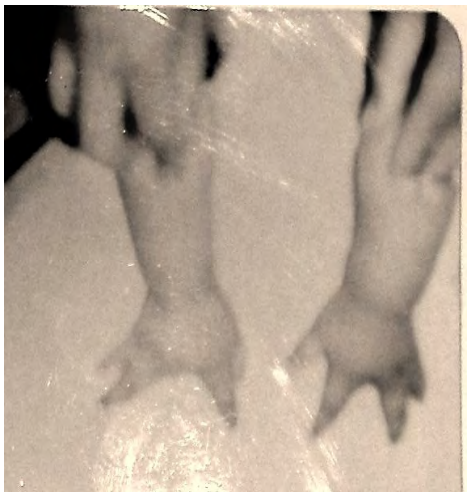

**Fig. 18:** Teratogenic split hand deformity and ectrodactyly.

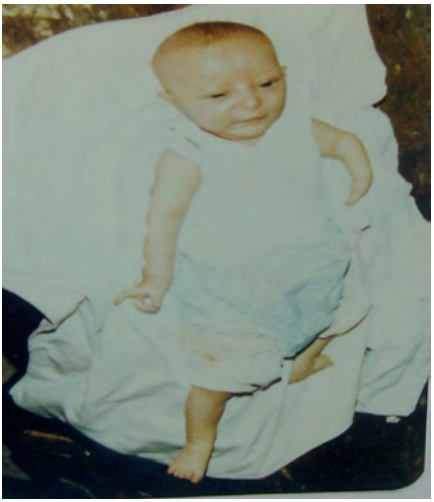

**Fig. 19:** Monodactyly of lt. hand and ectrodactyly of rt. hand in Hand- Heart syndrome type I.

## DISCUSSION

The results obtained from analysis of data of the current study reveals nothing new regarding the traditional known causes, types or pathological categories of limb defects observed among studied cases. However, it revealed that twenty four (24) cases constituting about (43.6%) of cases with isolated limb defects have clear and valid histories of maternal drug intake during the first trimester. Most catastrophic is prescription of progesterone preparations

as a prophylactic measure against early abortion. In two instances with severe deficient limb anomalies, the mothers began the therapy, as prescribed by their attending obstetricians, from the first month throughout the first 4 – 5 months of pregnancy and gave birth to a newborn with bilateral transverse hemimelia of the upper limbs in one case and a newborn with bilateral apodia in the other case. This iatrogenic, non-based evidence medical practice is, unfortunately, a common attitude among a considerable proportion of gynecologists and obstetricians taking care of pregnant women without any justification. It must be prohibited and physicians and medical care givers involved in health aspects of pregnant women should be alerted to the hazardous consequences of this wrong catastrophic practice.

Developing embryos and fetuses are quite sensitive to any biochemical/metabolic alterations in their intra-uterine environments. Bone growth and development responsible for setting up the whole body architecture is a very delicate and complicated process. Hence, it is amenable to marked quantitative and/or qualitative changes in response to slight changes in any of the metabolic networks that control its progression. These changes capable of disrupting and/or disturbing bone growth and development comprise many causative factors headed by drugs and chemicals in addition to many others like maternal metabolic status and infections.

Six teratogenic mechanisms associated with medication use have been delineated, they include: folate antagonism, neural crest cell disruption, endocrine disruption, oxidative stress, vascular disruption and specific receptor- or enzyme-mediated teratogenesis.[7]

Therefore, drug prescription to pregnant women in the first and second trimesters must be considered very seriously and with great care and recommended only where it proves indispensable for maternal health and well being.

The finding of a high rate of positive parental consanguinity in (47.3%) of cases with isolated limb defects, in (72.3%) of cases with syndromic limb defects and in (44.4%) of cases with limb defects due to chromosomal abnormalities elicits many querries when compared to previous data of parental consanguinity among Egyptians, estimated by many workers to fig around 28.9% in one study[8] to 33% in another study[9]. The high incidence of parental consanguinity in our study cases with isolated limb defects indicates the prominent operational effects of recessive genes in causation of a considerable portion of cases with isolated limb defects. This reasonable assumption demands a thorough counseling and meticulous clinical assessment of families with these cases in order to anticipate hazardous recurrence of similar cases via prophylactic measures, e.g antenatal screening and diagnosis.

## CONCLUSIONS

Though limb anomalies are unjustifiablty considered as accepted malformations as long as they are compatible with life, they actually represent a serious personal and social problem in view of their consequences on the ability of affected patients to earn their living and to accommodate with the society inspite of their cosmetic problems. Accordingly, sincere attention to the etiological factors, early diagnostic measures and preventive and curative procedures concerned with this catego-

ry of anomalies is important for affected patients, their families and the whole society as well.

Few, albeit, important recommendations could be drawn from the results of the current study. First, extremely cautious use of drugs during pregnancy must be always kept in mind by physicians taking care of pregnant women in view of the well established teratogenic effects of most drugs. Second, the high incidence of parental consanguinity in cases with isolated limb defects necessitates thorough counseling and meticulous clinical assessment in order to anticipate, detect and manage hazardous recurrence of similar cases via proper prophylactic approaches. Third and last, early and prompt intervention in cases of congenital limb defects is mandatory to save the patients and their families a lot of suffering due to the personal and social consequences of these anomalies and also to save the society the financial losses of man power due to the incapacitation induced by this category of congenital malformations.

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