Skeletal Manifestations in Patients with Genetic Disorders

Thesis

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By

Eslam Essam Mohamed Abo-Resha
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Under Supervision of

Prof. Dr. Rabah Mohamed Shawky
Professor of pediatrics and genetics
Faculty of Medicine – Ain Shams University

Prof.Dr. Solaf Mohamed Elsayed
Professor of Medical Genetics
Faculty of Medicine – Ain Shams University

Prof.Dr. Tamer Ahmed El-Sobky
Professor of Orthopedic surgery
Faculty of Medicine – Ain Shams University

Faculty of Medicine
Ain Shams University
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Introduction

The genetic disorders that can affect skeletal system are diverse. The many different forms add to produce a significant number of affected individuals with significant morbidity and mortality. They comprise a range of disorders affecting the spine, chest wall, the upper and lower extremities, the causes of which are complex, involving multiple factors that remain largely unknown. Skeletal manifestations can be classified into **limb abnormalities** which include absence deformities, brachydactly, syndactly, polydactly, clinodactly and arachnodactly. Limb anomalies can result from genetic abnormalities in the form of unbalanced chromosome abnormalities, in which there is a net gain or loss of genetic material or single gene mutations ***(Superti-Furga and Unger, 2007)***. **Chest wall deformities** which may be congenital or part of other genetic syndromes eg Morquio syndrome, Marfan and other connective tissue disorders. Rib cage overgrowth leads to depression of the sternum (pectus excavatum) or protuberance of the sternum (pectus carinatum) and accounts for greater than 90% of congenital chest wall deformities***(Nuss et al., 2005).*** **Spinal deformities** which includes Neural tube deformities, Congenital spine deformities due to failure of segmentation and Congenital spine deformities due to failure of formation ***(Kaplan, 2005).*** Spinal deformities may be congenital or may be part of other genetic syndromes eg, hereditary musculoskeletal disorders, such as osteogenesis

imperfecta, Marfan syndrome, Stickler syndrome, Ehlers Danlos syndrome, and the muscular dystrophies.

Early detection of any skeletal anomaly may be the guide line for many genetic syndromes also early detection of skeletal deformities give the chance for early intervention and prevention of complications if possible by medical treatment or even surgical treatment.

Aim of the Study

The aim of this study is to evaluate skeletal manifestation in patients with different genetic diseases both clinically and radiologically and to offer them the best medical and surgical management options.

Review of Literature

Genetic disorders

Definition: A genetic disorder is a genetic problem caused by one or more abnormalities in the genome. All diseases have a genetic component. Mutations may be inherited or developed in response to environmental stresses such as viruses or toxins.(**Gelehrter et al., 1998)**

Etiology: Genetic diseases can be due to

I): Chromosomal abnormalities classified into numerical and structural abnormalities.

II): Single gene disorders classified into autosomal dominant and recessive, X linked dominant and recessive.

III): Multifactorial diseases.

IV): Non mandelian inheritance (Non traditional).

Skeletal manifestations of genetic disorders

Skeletal manifestation are diverse, in this part we will stress on the common genetics disorders which have skeletal manifestations and includes,

1) Chromosomal abnormalities which is classified into

A): Numerical chromosomal abnormalities includes

- Autosomal chromosome: Down syndrome, trisomy 13, trisomy 18,
- Sex chromosomal: turner syndrome and kinefelter syndrome

B): Structural chromosomal abnormalities include

Wolf-Hirschhorn syndrome, 22q11.2 deletion syndrome, cri du chat syndrome and allagile syndrome

2) Single gene disorders classified into

a. Autosomal dominant disorders eg, achondroplasia, hypochondroplsia, pseudoachondroplasia, Marfan syndrome and Ehler danlos syndrome

b. Autosomal recessive disorders eg, Mucopolysaccharidosis type I and IV, gaucher disease, Osteogenesis imperfecta type II and III, Ehler danlos syndrome kyphoscoliotic type

c. X linked recessive disorders eg, Duchenne muscular dystrophy and Hunter syndrome

d. X linked dominant disorders eg, Vitamin D resistant ricket.

I): Chromosomal abnormalities

Can be classified into numerical and structural abnormalities

Numerical abnormalities which includes

1. Polyploidy which is the exact multiple of the halpoid number eg, triploidy and tetraploidy wich is a frequent finding in abortions (incompatible with life)

2. Aneuploidy which occur when an individual either is missing a chromosome (monosomy) (which may be autosomal which isn't compatible with life or sex chromosome eg, Turner syndrome, or has more than two chromosomes of a pair (trisomy) which may be autosomal eg; Trisomy 13&18&21 or sex chromosome eg, Klinefelter syndrome. Numeric and structural chromosomal abnormalities occur in approximately 0.6% of live births, 1 and often result in dysmorphism, malformations, ***(Shaffer et al., 2000)***

Numerical abnormalities of autosomal chromosomes

1) Down syndrome (DS)

Is the most common chromosome abnormality among liveborn infants. It is the most frequent form of intellectual disability caused by a microscopically demonstrable chromosomal aberration. DS is characterized by a variety of dysmorphic features, congenital malformations, and other

health problems and medical conditions. Not all of them are present in each affected individual. Dysmorphic features include upslanting palpebral fissures, epicanthic folds, and brachycephaly are nearly universal features of DS. The other characteristic dysmorphic features of DS are each present in 47 to 82 percent of cases (***Jones., 2006***). These features predominantly affect the head and neck and the extremities.

Characteristic dysmorphic features of DS affecting the head and neck include upslanting palpebral fissures, epicanthic folds, flat facial profile, low-set small ears, brachycephaly and short neck. Extremities, characteristic features of DS affecting the extremities include, short broad hands, incurved fifth finger with hypoplastic mid phalanx and wide space between the first and second toes (sandal gap).As regards radiological features found in cases with DS are diverse and affect many parts of the body, the skull shows brachycephalic microcephay, flat occiput and small posterior fossa, thin calvarium with wide suture and delayed closure of fontanels, hypoplasia of facial bone and sinuses, sphenoid hypoplasia ***(Stephen et al., 2010).***

The Spine shows, odontoid hypoplasia, atlantoaxial instability (figure 1) and dislocation, Atlantoaxial instability (AAI), defined as excessive mobility of the articulation of the atlas (C1) and the axis (C2), may lead to subluxation of the cervical spine. Approximately 13 percent of individuals with DS have asymptomatic AAI, while spinal cord compression due to the disorder affects approximately 2 percent (***Pueschel***

and Scola 1987). The diagnosis is made by lateral neck radiographs taken in neutral position, flexion, and extension. Patients with symptomatic spinal cord compression may have neck pain, torticollis, gait abnormalities, loss of bowel or bladder control, or signs of quadriparesis or quadriplegia and require immediate stabilization. Asymptomatic individuals appear to remain asymptomatic whether or not physical activity is restricted (***Juj and Emery 2009***). Also patients with down syndrome may exhibit, scoliosis, flattening of cervical vertebrae, arthritic changes of cervical vertebrae, increased height and decreased AP diameter of lumbar vertebrae. The pelvis may shows flared iliac wings with small acetabular angles, hip dysplasia and/or dislocation. Extremetis may show genu valgum, slipped capital femoral epiphysis, joint laxity and patellofemoral instability (**Dugdale, Renshaw 1986**).

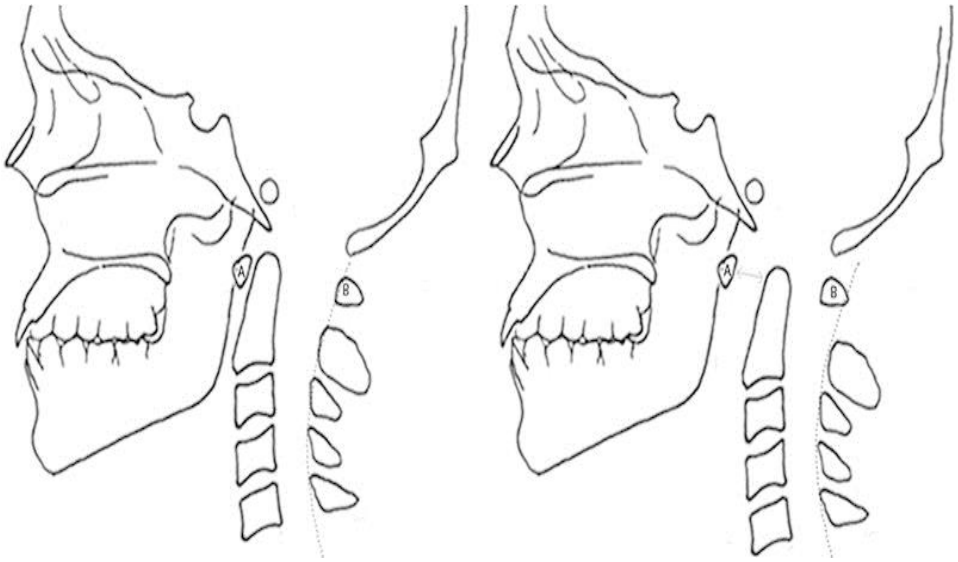

Figure (1): Schematic representation of atlantoaxial dislocation. Lateral view of the normal cervical spine in relation to the occiput (left) compared with an abnormal relationship between the cervical spine and occiput representing an atlantoaxial dislocation (right) ***(Yang et al., 2014)***

Down syndrome is characterized with short stature as growth rate is reduced in DS compared with typical children, especially in infancy and adolescence. Growth is most reduced in children with severe congenital heart disease. In adults with DS, the average height in males and females was 61.7 and 57 inches (157 and 144 cm), respectively, and the average weight was 157 and 140 lb (71 and 64 kg) in males and females in a 1998 study (***Rubin et al., 1998***).

2) Trisomy 18, also known as Edward's syndrome, is a common autosomal chromosomal disorder due to the presence of an extra chromosome 18. The syndrome pattern comprises a recognizable pattern of major and minor anomalies, an increased risk of neonatal and infant

mortality, and significant psychomotor and cognitive disability. The main clinical features represent the clues for the diagnosis in the perinatal period and include prenatal growth deficiency, characteristic craniofacial features, distinctive hand posture, overriding fingers, nail hypoplasia, short hallux, short sternum, and major malformations (particularly involving the heart) ***(Crider et al., 2003).*** Moreover Musculoskeletal Major malformations of limb occur in 5-10% of patients, including radial aplasia and other preaxial limb defects. About 50% of babies show positional foot deformities, both talipes equinovarus and calcaneovalgus. In addition, contractures of other joints can be present explaining why trisomy 18 is sometimes the basis for a neonate labeled arthrogryposis. Overriding fingers (second and fifth on third and fourth respectively) represent one of the important diagnostic clues, often detected sonographically in the prenatal period. Scoliosis is common in older children; usually it is not related to vertebral structural abnormalities and may progress between 5 and 10 years of age ***(Carey, 2010).***

3) <u>Trisomy 13 (Patau Syndrome)</u>

Patau syndrome is the least common and most severe of the viable autosomal trisomies. Although the major diagnostic criteria include microphthalmia, cleftlip/palate, and polydactyly, nearly every organ system may be involved. Ophthalmic abnormalities include colobomatous microphthalmia, colobomas,

cyclopia, cataracts, corneal opacities, glaucoma, persistent hyperplastic primary vitreous and retinal dysplasia. (**Patau et al., 1960**)

Numerical abnormalities of sex chromosomes

1) Klinefelter syndrome(KS)

The classic form of KS, which is present in the 80–90 **%**of the cases, is defined by a 47, XXY karyotype resulting from the aneuploidy of the sex chromosomes, whereas higher-grade aneuploidies (e.g. 48, XXXY or 48, XXYY**(**, structurally abnormal X chromosome (e.g. 47, iXq, Y) or mosaicisms (e.g. 47, XXY/46, XY) make up approximately in the remaining 10–20 % of cases. As traditionally described, patients with KS have tall stature, small testes, gynecomastia in late puberty, gynoid aspect of hips (broad hips), sparse body hair, signs of androgen deficiency and low serum testosterone coupled with elevated gonadotropins, and finally azoospermia, oligospermia with hyalinization and fibrosis of the seminiferous tubules between the ages of 15 and 30 years. So skeletal manifestations in patients with KS include tall stature, gyncoid shaped pelvis and osteoporosis. Osteoporosis incidence in klinefelter syndrome patients reaches about 10% which results in an increased incidence of bone fractures; femoral fractures which are associated with a high mortality rate ***(Gravholt et al., 2011)***

2) <u>Turner syndrome</u>:

A disorder in females characterized by the absence of all or part of a normal second sex chromosome, leads to a constellation of physical findings that often includes congenital lymphedema, short stature, and gonadal dysgenesis. Approximately half have monosomy X (45, X0), and 5 to 10 percent have a duplication (isochromosome) of the long arm of one X (46, X, i(Xq)). Rest of the cases have mosaicism for 45, X, with one or more additional cell lineages.(**Suri et al., 1995)**

Musculoskeletal characteristics of Turner syndrome include skeletal dysplasia, with short stature, mild epiphyseal dysplasia, and typical bony alterations, dislocation of the patellae and chronic knee pain. Malformation of the ulnar head causes the typical increased carrying angle of the arm and may cause limited range of motion. Chondrodysplasia of the distal radial epiphysis (Madelung's deformity), typical of the Leri–Weill syndrome -the skeletal dysplasia associated with *SHOX* haploinsufficiency is a rare complication. Congenital dislocation of the hip is common occurring in 5 percent of patients, while clinically significant scoliosis occurring in 10 percent ***(Wiley-Liss, 2001)***. Clinical manifestations induced by Madelung deformity include wrist pain, deformation and limited joint motion.Radiological findings of Madelung deformity include the absence or narrowing of the ulnar portion of the distal radial physis, anterior bowing of the radial shaft and dorsal subluxation of the ulnar head.

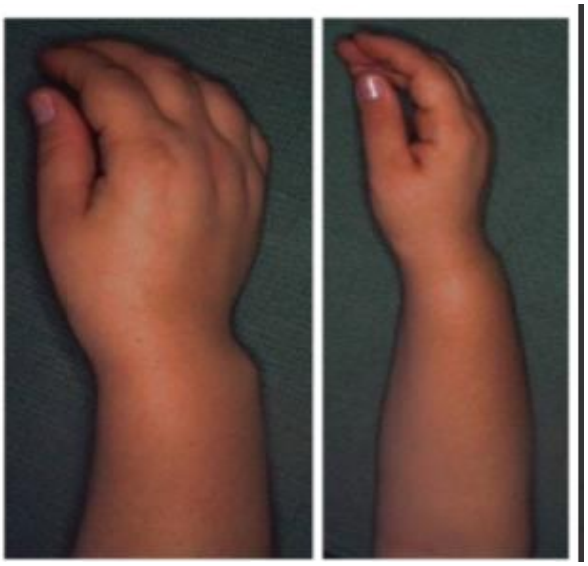

Figure (2): Show madelung deformity.(**David et al., 2016**)

1) Structural abnormalities includes

1) **Deletion.** It is a breakage in the chromosome, leads to loss of small broken chromosome piece. It may be terminal, interstitial or ring (r). Known disorders of deletions include **Wolf-Hirschhorn syndrome**, which is caused by partial deletion of the short arm of chromosome 4 and **The Cri du Chat syndrome** (CdCS) which results from a deletion of variable size occurring on the short arm of chromosome 5 (5p-).(**Lejeune et al., 1963)**

2) **Inversion.** When a chromosome breaks and the piece of the chromosome turns upside down and reattaches itself. Inversions may or may not cause birth defects depending on their exact structure. It may be peri-centric or para-centric.