A Comparative Study of the Frequency of Occurrence of Genetic Skeletal Disorders in Iraq before and after the Second Gulf War, 1991

Bassam Musa Sadik, Selma A.H. Al-Taha

ABSTRACT:

BACKGROUND:

Genetic skeletal abnormalities are a heterogeneous group of genetic disorders frequently presenting with disproportionate short stature.

AIM OF THE STUDY:

To give an idea about the frequency of genetic skeletal abnormalities, and to find out whether these disorders are really increasing in the last 16 years or not.

METHODS:

During the period extending from (Jan, 1st 2003-April, 1st 2007), all cases of genetic skeletal disorders referred to the Genetic Counseling Clinic, Medical City – Baghdad who were born after 1991 were included in this study as the post-war group; the pre-war group, included all cases of skeletal disorders referred prior to 1991 (Jan., 1st 1987-Jan., 1st 1990). The demographic parameters, family history of the disease plus the parental consanguinity were studied.

RESULTS:

The post-war group constituted 3.199% while the pre-war group constituted 2.815%. Both groups had a comparative age range. AR disorders constituted 39.75% of the post-war group and 40% in the pre-war group; AD disorders come next in both groups (37.3% vs. 33.8%) respectively. There is a noticeable increase in the occurrence of new mutations of AD disorders in the post-war group.

CONCLUSION:

Genetic skeletal dysplaisas are not uncommon disorders; their incidence seems to be truly increasing.

KEYWORDS: Genetic Skeletal Disorders, Frequency of Occurrence, Second Gulf War, Iraq.

INTRODUCTION:

Genetic skeletal dysplasias are a heterogeneous group of genetic disorders associated with abnormalities in the skeletal system frequently presenting with disproportionate short stature. There are over 200 distinct skeletal dysplasias which have been classified primarily on the basis of the clinical or radiographic characteristics [1].

Skeletal dysplasias can be broadly classified into two main groups:

osteochondrodysplasias and dysostoses [2].

I- **The Osteochondrodysplasias,** in which there is, generalized abnormality in bone or cartilage. This group is subdivided into three main categories:

- Defects of the growth of tubular bones and or spine (chondrodysplasias).
- Abnormalities of density or cortical diaphyseal structure and or metaphyseal modeling.
- Disorganized development of cartilage and fibrous components of the skeleton.

II- **Dysostoses:** This group refers to malformations or absence of individual bones singly or in combination. They are mostly static and their malformations occur during blastogenesis (1st 8 weeks of embryonic life).

Dept. of Pathology, College of Medicine, Baghdad Univ.

This is in contrast to osteochondrodysplasias, which often present after this stage, has a more general skeletal involvement and continue to evolve as a result of active gene involvement throughout life [3]. The dysostoses group can be sub-classified into three main categories:

- Those primarily concerned with craniofacial involvement and includes in various craniosynostosis.
- Those with predominant axial involvement including the various segmentation defect disorders.
- Those affecting only the limbs [2].

Although the skeletal dysplasias are individually rare, the collective total is substantial, and greater, for example, than the number of haemophilic patients in Britain [4]. As a group or category of disorders, skeletal dysplasias are common, occurring with a birth prevalence of 1 in 4,100. There is a high rate of stillborns (23%) and early postnatal death (32%), indicating an acute need for correct diagnosis and appropriate intervention strategies [5]. Diagnosis of Skeletal Dysplastic conditions are suspected on the basis of abnormal stature, disproportion, dysmorphism, or deformity. Diagnosis requires simple measurement of height and calculation of proportionality, combined with a

complete physical examination, appropriate radiographs, an investigation of the family pedigree, and occasionally laboratory studies [6].

In light of the recent advances in molecular genetics, however, many phenotypically similar skeletal diseases comprising the classical categories turned out not to be based on defects in common genes or physiological pathways [7].

Generally all skeletal dysplasias warrant multidisciplinary attention. Regular assessment by an orthopedist, geneticist, pediatrician, dentist, neurologist, and physical therapist will provide the most comprehensive treatment [8].

The number of recognized genetic disorders with a significant skeletal component is growing and the distinction between dysplasias, metabolic bone disorders, dysostoses, and malformation syndromes is blurring. For classification purposes, pathogenetic and molecular criteria are integrating with morphological ones but disorders are still identified by clinical features and radiographic appearance [9]. In Iraq, few studies came across the incidence of congenital malformation including skeletal abnormalities [10, 11], the most interesting was that published in 2002 that mentioned a noticeable increase in the incidence of these disorders along with other genetic and congenital disorders after the second gulf war as compared to the prewar period [12]. However, in these studies, no detailed information was mentioned in regard to the incidence of each type pf skeletal dysplasia and other genetic syndromes that cause skeletal abnormalities.

AIM OF THIS STUDY:

Our aim in this retrospective study is to give as accurate as possible the frequency of occurrence of skeletal abnormalities in general as well as knowing the most common disorders encountered on one hand, and finding whether these disorders are truly increasing in the last 16 years as compared to the prewar period or not on the other hand.

PATIENTS AND METHODS:

During the period of four years and three months (Jan, 1st 2003-April, 1st 2007), all cases referred to the Genetic Clinic, Consultation Clinics, Medical City Institute – Baghdad and were diagnosed as having one form of genetic skeletal disorder and were born following the 2nd Gulf war, 1991 were included in this study as the post-war group. Another group of cases, the pre-war group, included all cases of skeletal disorders referred prior to 1991 (Jan., 1st 1987-Jan., 1st 1990) to the genetic clinic. All cases were diagnosed following a history taking and clinical examination and the appropriate radiographic examination.

Cases excluded from the study were those with a known chromosomal disorder leading to short stature (e.g. Turner's syndrome), nutritional and endocrine causes, and those with constitutional short stature and those cases resulting from teratogenic effect of certain drugs, in utero posturing or amniotic band.

The demographic parameters for each case were assessed; family history of the disease plus the parental consanguinity was also established. Genetic counseling was made and a report was given to each case for the referring physician or surgeon. The pre-war group was compared to the post-war group in regard of the above parameters.

RESULTS:

A study of the frequency of occurrence (FOC) of skeletal abnormalities in a sample of Iraqi cases referred to the Genetics Clinic, Consultation Clinics, Medical City Institute – Baghdad in two periods each lasting 4 years or more was performed in this study. It is of importance to mention that the frequency of occurrence rather than the incidence of these disorders was mentioned here as this study included only the referred cases to the genetics clinic and not the total affected cases out of total births in Iraq. Yet, this sample is still representative of the actual burden of these disorders in this country, as the referral of cases reflects how much cases were seen in different hospitals and in different specialties. A total of 2594 cases were referred to the genetics clinic during the period of 51 months (from Jan., 1st 2003 till April, 1st 2007) (the post-war group), with an age ranging from a second trimester abortuses till 15 years, all born after 1991, while the pre-war group included 2309 cases referred during the period of 4 years (Jan., 1st 1987-Jan., 1st 1990) with an age range from a third trimester abortus-13 years. From the 2594 referred cases in the post-war group, 83 cases were diagnosed as having one type of skeletal dysplasias or a known genetic syndrome causing an evident skeletal abnormality with a frequency of occurrence of (3.199%), while cases of the pre-war group constituted 65 out of 2309 (2.815%); Tables (1, 2). Male to female ratio in the post-war group was 1.19:1, while that in the pre-war group was 0.65:1; Tables (1, 2). The mode of inheritance and the family history (FH) of the disorder in both groups is shown in Tables (3,4). It was noted that autosomal recessive (AR) disorders were the most frequently occurring disorders in both groups, while the autosomal dominant (AD) disorders come next, then the sporadic cases and lastly the X-linked disorders; Tables (3, 4).

Table (5) shows all disorders causing genetic skeletal abnormalities in both study groups and their frequency.

Table 1: Distribution of cases of skeletal abnormalities according to the year of referral, gender, and frequency of occurrence among the post-war group

Year	Male	Female	?	Total No. affected	Total No. referred	FOC
2003	10	9	1	20	476	4.201%
2004	5	1	1	7	692	1.011%
2005	10	8	0	18	666	2.702%
2006	13	14	0	27	680	3.970%
2007	6	5	0	11	80	13.75%
Total	44	37	2	83	2594	3.199%

= an abortus whose gender was not determined
= included only the first 3 months whenever it is mentioned

Table 2: Distribution of cases of skeletal abnormalities according to the year of referral, gender, and frequency of occurrence among the pre-war group

Year	Male	Female	?	Total No. affected	Total No. referred	FOC
1987	3	6	0	9	518	1.737%
1988	7	10	1	18	723	2.489%
1989	4	10	0	14	689	2.031%
1990	9	12	3	24	379	6.332%
Total	23	38	4	65	2309	2.815%

= an abortus whose gender was not determined

Table 3: Distribution of skeletal abnormalities cases in the post-war group according to the mode of inheritance and family history

Year	AD	AR	X-linked	Sporadic	Total	-ve FH	+ve FH
2003	6	10	1	3	20	17	3
2004	2	4	0	1	7	4	3
2005	3	10	2	3	18	12	6
2006	13	8	0	6	27	19	8
2007	7	1	0	3	11	9	2
Total	31	33	3	16	83	61	22

Table 4: Distribution of skeletal abnormalities cases in the pre-war group according to the mode of inheritance and family history

Year	AD	AR	X-linked	Sporadic	Total	-ve FH	+ve FH
1987	2	4	0	3	9	9	0
1988	6	5	0	7	18	14	4
1989	5	6	0	3	14	12	2
1990	9	11	0	4	24	22	2
Total	22	26	0	17	65	57	8

Table 5: Frequency of occurrence of the most common genetic skeletal abnormalities in both groups

No.	Disorder Causing Skeletal Deformities	Post-war group	Prewar group	Total
1	Achondroplasia Syndromes (All Types)	6	7	13
2	Russell Silver Syndrome	8	1	9
3	Craniosynostosis (Saethre-Chotzen, Crouzon, Pfieffer, Carpenter)	1	7	8
4	Metaphyseal Chondrodysplasia (Kniest, Mckusick, Schmid, Jansen)	4	3	7
5	Morquio Type of Mucopolysacchraidosis	6	0	6
6	Hypochondroplasia Syndrome	4	2	6
7	Seckel (Bird-Headed) Dwarfism	2	4	6
8	Ellis-Van Creveld Syndrome	4	1	5
9	Klippel Fiel Syndrome	4	1	5
10	Thanatophoric Dwarfism Syndrome	3	1	4
11	Achondrogenesis	2	2	4
12	Smith Lemli Opitz Syndrome	2	2	4
13	Cornelia De Lange Syndrome	1	3	4
14	Osteogenesis Imperfecta (All Types)	2	1	3
15	Saldino Noonan Syndrome	2	1	3
16	Oral Facial Digital Syndrome (Both Types)	1	2	3
17	Hurler's Type of Mucopolysacchraidosis	1	2	3

18	Rubenstein Taybi Syndrome	2	0	2
19	Osteochondrodysplasia (Pseudo-Vitamin D-Deficiency Rickets)	2	0	2
20	Hallermann Streiff Syndrome	1	1	2
21	Osteopetrosis	1	1	2
22	Vitamin-D Resistant Rickets	1	1	2
23	Type I Glycogen Storage Disease (von Gierke)	1	1	2
24	Robinow Syndrome	1	1	2
25	Treacher Collins Syndrome	1	1	2
26	Leri Weill Dyschondrogenesis Syndrome	1	0	1
27	Coffin Lowry Syndrome	1	0	1
28	Hair Cartilage Syndrome (Mckusick)	1	0	1
29	Tricho-Rhino-Phalangeal Syndrome	1	0	1
30	Oculo-Dento-Digital Syndrome	1	0	1
31	Oto-Palato-Digital Syndrome	1	0	1
32	Cleido-Cranial Dysostosis	1	0	1
33	Fronto-Nasal Dysplasia	1	0	1
34	Albright Hereditary Osteodystrophy (PseudoHypoparathyroidism)	1	0	1
35	Johnason Blizzar Syndrome	1	0	1
36	Mucolipidosis Type Ii (Leroy I-Cell Syndrome)	1	0	1
37	Brachydactyly Syndrome	1	0	1
38	Facio-Costo-Chondral Dysostosis	1	0	1
39	Sclerostosis	1	0	1
40	Facio-Auriculo-Vertebral Anomalad (Goldenhar Syndrome)	1	0	1
41	Tricho-Dento-Osseous Syndrome	1	0	1
42	Spondylo-Epiphyseal Metaplasia	1	0	1
43	Sanfilippo Type Mucopolysacchraidosis	1	0	1
44	Rhizomelic Chondrodysplasia Punctata Syndrome	1	0	1
45	Multiple Epiphyseal Dysplasia	1	0	1
46	Maroteaux-Lamy Type of Mucopolysacchraidosis	0	1	1
47	Blepharo-Facial Dysostosis	0	1	1
48	Asphyxiating Dwarfism	0	1	1
49	Oro-Acral Dysostosis	0	1	1
50	Metatropic Dwarfism	0	1	1
51	Nivergelt Syndrome	0	1	1
52	Springle Syndrome	0	1	1
53	Mucopolysacchraidosis (type was not specified)	0	6	6
54	Undefined Cases	0	6	6
	Total	83	65	148

DISCUSSION:

In the past three decades many more of skeletal disorders have been identified. Incidence at birth, expressed as a figure per 10,000 or 100,000 births, takes no account of the many skeletal dysplasias which become manifest later in childhood or even in adult life; neither can the severity of the disorder be adequately assessed at birth, nor the possibility of early death (other than perinatal) be taken into account [4]. Yet, it is possible to make an estimate of the minimum number of affected individuals in the country and, more accurately, of the number requiring genetic counseling. Our results showed that the incidence of cases of genetic skeletal dysplasias among all genetic disorders referred to the genetics clinic in the post-war group was 3.199% as compared to 2.815% in the pre-war group. This increase in the incidence of referred cases might be a reflection of a true increase in the incidence of these disorders in the last 16 years or may be biased from the influence of other factors; but when comparing these results with that obtained from a previous Iraqi study, which showed an increase in their incidence from 2.79% in the pre-war group to 3.568% in the post-war group [12], we can consider these figures as truly indicative of an actual increase in its incidence. Moreover, 2 previous Iraqi studies conducted in Baghdad and Basrah in 1994 [10, 11] have shown an incidence of skeletal abnormalities of 1.07% and 0.25% respectively, which when compared to our results of the post-war group, a more convincing evidence can be obtained in regard to this conclusion. However, this observation can only be strengthened or disputed in the view of a thorough study with a larger study group in different pediatric and orthopedic hospitals in addition to the genetic counseling clinic conducted in different governorates of Iraq to highlight the actual figures

of the incidence of genetic skeletal disorders. Male to female ratio was found to be 1.19:1 in the post-war group vs. 0.65%:1 in the pre-war group.

This minor difference in the post-war group can be explained by the presence of 3 cases of X-linked disorders in this group. On the other hand, female preponderance in the pre-war group is of no clinical importance as it might be a matter of coincidence. In regard to the mode of inheritance, autosomal recessive (AR) disorders constituted (39.75%) of the post-war group, which is quite similar to that in the pre-war group was (40%), while autosomal dominant (AD) disorders come next in both groups (37.3% vs. 33.8%) respectively. This is followed by the sporadic cases (19.2%) in the post-war group vs. (26.15%) in the pre-war group. This is due to a group of AR skeletal disorders, namely (Ellis van Creveld, mucopolysaccharidoses... etc.), (Table 5), that are more common than other AD or sporadic syndromes. The sporadic cases are logically less common that AR or AD disorders but those cases plus the AD disorders with a negative family history (-ve FH) are those cases that require special attention and a comparison should be made between the pre-war and the post-war groups, as they reflect the amount of environmental pollution and the degree of new mutations occurring in the newer generations. Thus, this study has focused on this fact to support or dispute the observation made earlier [12]. The percentage of cases with a –ve FH in the post-war group as compared to that in the pre-war group was (73.49% vs. 87.69%) respectively. Yet, this represents all AR, AD and the sporadic cases. If we excluded AR cases and the sporadic cases, the latter by definition occur once in a family (and thus already expected to have a –ve FH), we find that the AD disorders with a –ve FH constitutes the majority of the single cases encountered in the post-war group that are not found in the pre-war group (no. 27-47 in table 5) (new fresh mutations), while the majority of those occurring once in the pre-war group and none in the post-war group are AR and sporadic disorders. This, in fact, strengthens the observations made in 2002 earlier [12]. Table (5) shows the most common skeletal disorders encountered in this study and shows that achondroplasia lies first, which is in agreement of what mentioned in other articles that achondroplasia is the most common non-lethal skeletal dysplasia [13].

In regard to the lethal types of skeletal dysplasias in our study, thanatophoric dysplasia and achondrogenesis lie in the 10th and 11th rank of our list, in contrast to what was mentioned in other studies [13], which mentioned that they account for 62% of all lethal skeletal dysplasias.

This difference is the result of that fact that most cases referred to the genetics clinic are young children with skeletal problem and rarely abortuses unless they have a positive family history of recurrent abortion or stillbirth.

It is noticed that mucopolysaccharidoses as a group are frequently encountered all the time, especially type IV (Morquio), and when counted altogether, they come 1st in our list. This is due to aggregation of cases in our study.

CONCLUSION:

Genetic skeletal dysplaisas are not uncommon disorders and their incidence seems to be increasing, probably due to the effect of increasing environmental pollution after the 2nd Gulf war till now, an observation that needs to be further documented on a larger scale study.

REFERENCES:

1. Wasant P, Waeteekul S, Rimoin DL, Lachman RS. Genetic skeletal dysplasia in Thailand: the Siriraj experience. Southeast Asian J Trop Med Public Health. 1995; 26 Suppl 1: 59-67.
2. Temtamy SA. McKusick VA. The Genetics of Hand Malformations. New York, Alan R Liss, Inc., for the National Foundation-March of Dimes. (1978) [reprinted in 1987 and in 2001]. BD:OAS XIV 3.
3. Sillence DO. Disorders of bone density, volume and mineralization. In Emery and Rimoin's Principles and Practice of Medical Genetics. (2002). 4th edition. Rimoin DL, Connor JM, Pyeritz R, Korf B (editors). Edinburgh: Churchill-Livingstone. 4115-6.
4. Wynne DR, Gormley J. The prevalence of skeletal dysplasias. An estimate of their minimum frequency and the number of patients requiring orthopaedic care. British Editorial Society of Bone and Joint Surgery. January 1985; 67-B,133-7.
5. Nelson, J.; Crowhurst, J.; Carey, B.; Greed, L. Incidence of the mucopolysaccharidoses in Western Australia. Am. J. Med. Genet. 2003; 123A: 310-313.
6. Rodney KB, William H. Skeletal Dysplasias: An Approach to Diagnosis. J Am Acad Ortho Surg. May/June 1995; 3.
7. Uwe K and Stefan M. Genetic Disorders of the Skeleton: A Developmental Approach Am J Hum Genet. 2003; 73: 447–474.

8. Montano AM, Tomatsu S, Gottesman GS, Smith M, Orii T. International Morquio A Registry: clinical manifestation and natural course of Morquio A disease. J Inherit Metab Dis. 2007; 30:165-74.

9. Andrea SF, Sheila U. Nosology and Classification of Genetic Skeletal Disorders: 2006 Revision. American Journal of Medical Genetics Part A 143A:1–18; 2007.

10. Habeeb SI. The incidence of congenital malformation and associated risk factors in Basrah City. A thesis submitted for the Iraqi Commission for Medical Specialization in Pediatrics, 1994.

11. Hadid ZA. The incidence of congenital malformation. Diploma thesis in Paediatrics submitted to the College of Medicine, Baghdad University, 1994.

12. Selma AH Al-Taha. The effect of depleted uranium and war pollution on Iraqi generation. J Fac Med (Baghdad), 2002; 44, 990-6.

13. Baitner AC, Maurer SG, Gruen MB, Di Cesare PE: The genetic basis of the osteochondrodysplasias. J Pediatr Orthop 2000; 20: 594-605 [Medline].