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Research Article

Cutis laxa with growth and developmental delay, wrinkly skin syndrome and gerodermia osteodysplastica: A report of two unrelated patients and a literature review

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Abstract

Two unrelated patients of different sexes are described, both presenting with congenital redundant skin (cutis laxa), growth deficiency, mental retardation and bone dystrophy. Parental consanguinity in both families and a more pronounced severity of the neurological disease in the male patient were present. Both patients were diagnosed in infancy as having De Barsy syndrome, but clinical follow-up revealed that the clinical picture was compatible with the diagnosis of cutis laxa with growth and developmental delay (CLGDD), gerodermia osteodysplastica (GO) and wrinkly-skin syndrome (WWS). It has recently been suggested that cutis laxa with growth and developmental delay, gerodermia osteodysplastica and wrinkly skin syndrome are the same condition. A review concerning this diagnosis is also presented.

Key words: cutis laxa, De Barsy syndrome, gerodermia osteodysplastica, wrinkly skin syndrome.

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Introduction

Congenital redundant skin has been variously described as chalazoderma, dermatochalasis, pachydermatocele, dermatomegaly, dermatolysis, primary elastolysis, generalized elastolysis, edema elastolyticum, cutis laxa and wrinkly skin. All these terms describe loose skin hanging in different parts of the body and conferring a senile aspect to the individual.

Debré *et al.* (1937) first used the term 'cutis laxa with bone dystrophy', currently called 'cutis laxa with growth and developmental delay' (CLGDD; OMIM 219200), to describe a rare condition characterized by redundant loose skin, pre- and post-natal growth deficiency, mental retardation, large fontanels, hip dislocation and dysmorphic facial features, as well as radiological signs consisting of osteoporosis and Wormian bones. Histological findings include aggregation, fragmentation and clumping of elastic fibers.

Bamatter *et al.* (1950) created the term 'gerodermia osteodysplastica' (GO; OMIM 231070) to describe a prematurely aged appearance associated with skeletal findings of osteoporosis, vertebral deformity and fractures. The term can also be written as 'geroderma osteodysplasticum' (Wiedemann, 1978). Its main clinical features are lax and wrinkled skin, especially on the dorsum of the hands and feet, dysmorphic facial features, joint hyperextensibility, global developmental delay in many cases and radiological manifestations including Wormian bones, with intra- and interfamilial variability (Al-Gazali *et al.*, 2001). Histological features include excessive fragmentation of the elastic fibers (Lisker *et al.*, 1979).

Gazit *et al.* (1973) coined the term 'wrinkly skin syndrome' (WSS; OMIM 278250) to describe a condition following autosomal recessive inheritance and comprising lax, wrinkled skin over the dorsum of the hands and feet, wrinkled abdominal skin in the sitting position, an increased number of palmar and plantar creases, hip dislocation, intrauterine growth retardation, growth failure and developmental delay. Some facial dysmorphic features have been reported but data on radiological findings are scarce. Histological studies describe distorted and fragmented elastic fibers (Boente *et al.*, 1999).

In 1999, Zlotogora proposed that CLGDD and WSS might represent the same disorder. More recently, the clinical overlap between WSS and GO has been noted and the

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same connection proposed (Al-Gazali *et al.*, 2001). The clinical overlap in these diagnoses was noted early on and many authors reported patients under one term, citing the other terms as differential diagnoses. A few clinical findings have been used to justify the use of one term in preference to the other terms. In GO, for example, alterations of the upper to lower body segment, probably due to platyspondyly, and absence of visible superficial veins were used to differentiate GO from cutis laxa. It is interesting to note that some findings are more frequently described using one term than another. Large fontanels are a constant anomaly reported in CLGDD and in many GO cases but were described in only one patient diagnosed with WSS, while increased palmar creases are a constant finding in WSS but are not mentioned in the reports of CLGDD. In GO, the term 'Walt Disney dwarfism' has been used in several reports (especially the initial reports), which has influenced many of the subsequent authors. This may be an example of authorial description bias in which clinical reports tend to be based on and compared to previous descriptions.

Until now, the most common designation is "cutis laxa", which refers to a heterogeneous group of disorders of the skin. Zlotogora (1999), however, suggested the use of "wrinkly skin syndrome" and dismissed the term "cutis laxa with growth and developmental delay", suggesting that these patients do not present a true form of cutis laxa.

We describe two unrelated patients with features compatible with CLGDD, GO and WSS and also present a literature review on this theme.

Clinical Reports

Patient 1

A male, born at term after an uneventful pregnancy and delivery, is the only child of healthy, young first-cousin parents of Portuguese, Afro-Brazilian and Amerindian ancestry. His birth weight was 2,100 g, birth length 41 cm, OFC 29 cm (all below the 3rd centile) and the Apgar score was 7/8. At the first clinical examination at 15 days of age he was noted to have a senile facial appearance. The skin was thin and appeared aged, especially in the face and periorbital region, and was loose in the nape of the neck, trunk and extremities. There were excessive creases in the palms and soles and superficial blood vessels were visible under the thin skin. Other features included a prominent occipital, high forehead, triangular face, anteverted ears with slight hypoplasia of auricular lobes, epicanthal folds, blue sclera, small nose, micrognathia, long philtrum, thin lips, short neck and diastase of the abdominal muscles. Wrists and proximal interphalangeal joints were in flexion, permitting painful extension, and the toes were long. Subcutaneous tissue was scanty and loose (Figure 1). Evolution in the first year of life showed accentuation of the senile aspect and psychomotor delay with axial hypotonia. At 17 months of age the anterior fontanel was still open and measured 4 x 6 cm and an inguinal hernia was also observed. The teeth were small, yellow and cone shaped. At 5 years of age he weighed 11,500 g and was 92 cm tall (both below the 3rd centile); the OFC was 51 cm (50th centile) suggesting relative macrocephaly. Clinical follow-up revealed exacerbation of the senile appearance, especially in the dorsa of the hands and feet, and the presence of umbilical and inguinal hernias, retractile testes, genu valgum and flat feet; venous prominence became less evident with age and prognathism was present. Joint mobility was considered normal and there was no upper-lower segment disproportion. He had two fractures of the right forearm after trauma. The patient has mental impairment with hyperactivity and attends a school for handicapped children. At the age of 10, senile aspect of the face and hands was striking (Figure 2). Complementary studies were normal and included chromo-

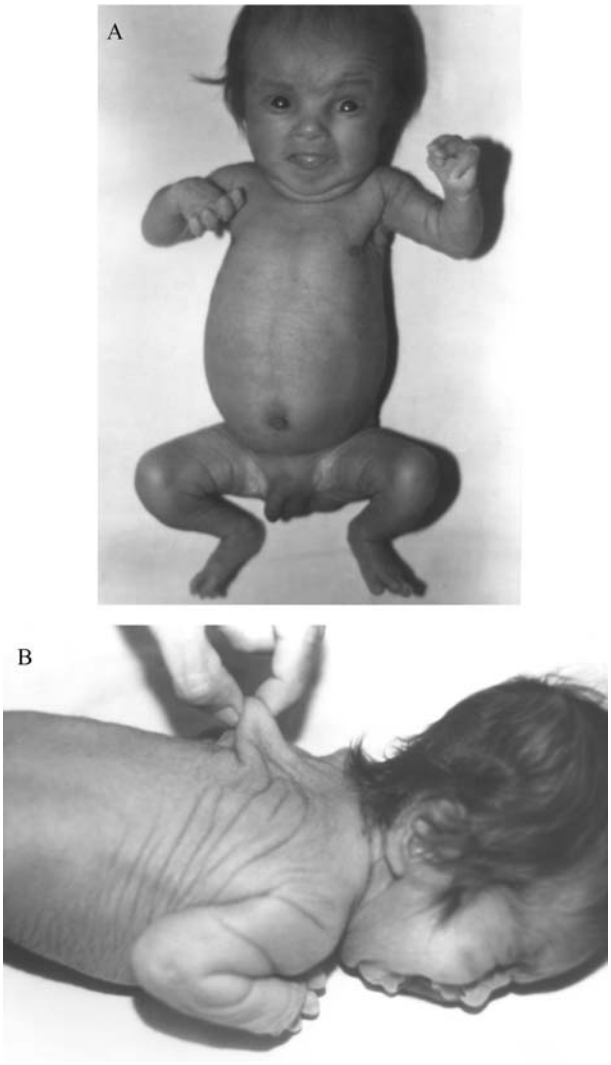

Figure 1 - Patient 1 at 4 months of age. Note the senile appearance and abnormal position of the hands (A) and hyperextensible skin on the dorsum (B).

somal analysis using lymphocyte G-banding (500 bands), amino acid chromatography, EEG, cardiologic and ophthalmologic evaluations. Echoencephalography showed mild hydrocephalus and scintigraphy revealed diminished glomerular function. Radiological exams revealed Wormian bones, scoliosis, osteoporosis, and bladder diverticula. Platyspondyly was not present until the last evaluation.

Patient 2

A female, the 2nd child of first-cousin parents of Portuguese, Afro-Brazilian and Amerindian ancestry. She was born at term by caesarean section after an uneventful pregnancy. Her birth weight was 1,460 g, birth length 39 cm and the OFC was 31 cm (all below the 3rd centile). At the first clinical examination at four months of age she appeared aged with cutis laxa over the trunk, nape of the neck and extremities, and had thin skin and prominent blood vessels. Her weight was 3,550 g, length 52.5 cm and she had a 37 cm OFC (all below the 3rd centile). She also presented high forehead, open cranial sutures, dysmorphic ears, small and thin nose, high narrow palate, chest asymmetry, fovea coccigea, umbilical and right inguinal hernias, abnormal positioning of the fingers and toes, hyperextensibility of the small joints, hypoplasia of the labia majora and sparse and thin hair. At 6 months of age hip dislocation and muscular hypotonia were noted. The anterior fontanel closed when she was 2 years old. At 3 years of age she was still unable to stand (Figure 3). At 10 years old she was short in stature and presented scoliosis, lumbar lordosis and weak abdominal muscle tone, prognathism started to be apparent and the fingers and toes were still in abnormal positions (Figure 4). Neuropsychomotor development was delayed and, like patient 1, she presents learning disabilities. Menarche occurred at the age of 9, with regular cycles to date. She has no history of fractures and no upper-lower segment disproportion. Complementary studies included standard chromosomal analysis, amino acid chromatography, urinary hydroxyproline, echoencephalography, EEG, cardiologic and ophthalmologic evaluation, all with normal results. Radiological findings were Wormian bones, bilateral hip dislocation, proximal shortening of the radius and bladder diverticula. Platyspondyly was not seen up to the last radiological evaluation.

Histology

Cutaneous biopsies of the buttocks were taken from both patients and histological examination showed that in both individuals the epidermis was almost twice the thick-

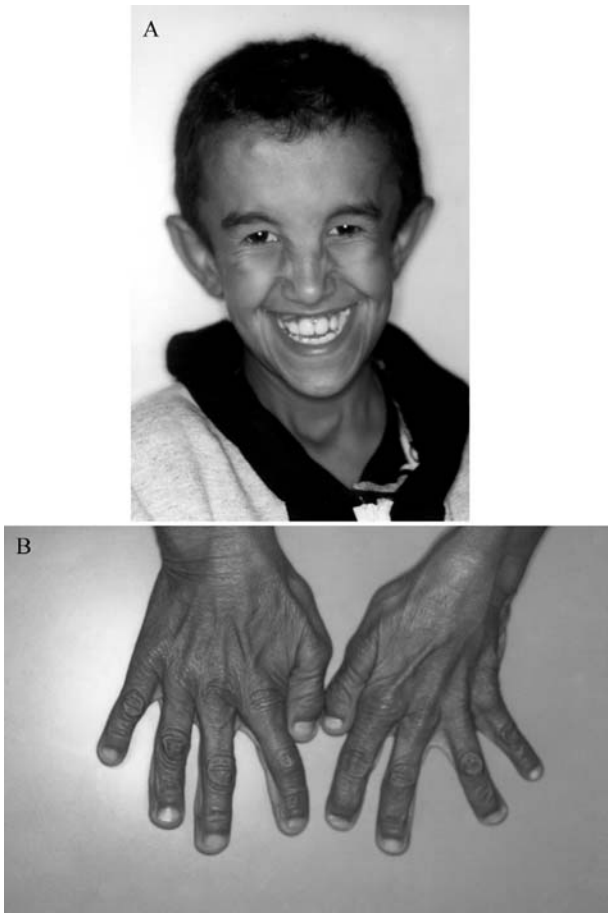

Figure 2 - Patient 1 at 10 years of age. Note the senile aspect of the face (A) and hands (B).

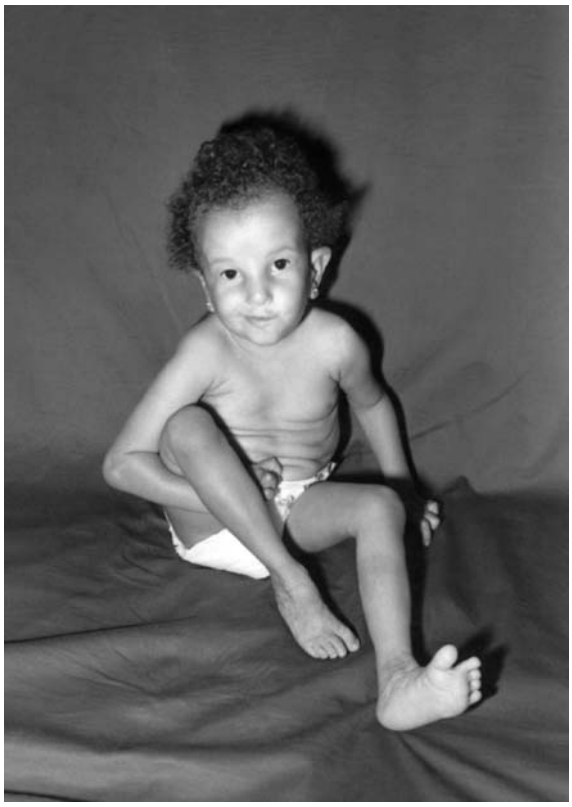

Figure 3 - Patient 2 at 3 years of age, still unable to stand.

ness of control values while the dermis was almost half the thickness of control values (Table 1). The Weigert Van Gieson stain showed a reduction in the amount of elastic fibers, which were short and fragmented. Electron microscopy (Figure 5) showed apparently normal collagen but in patient 1 the elastic tissue appeared as scattered and irregular aggregates of dark material while in patient 2 the small elastic fibers were sparse.

Discussion

The patients were referred to us in the first months of life because of redundant skin giving them a senile appearance. De Barsy syndrome was the first diagnosis considered, this being an autosomal recessive condition sharing many similarities with other forms of cutis laxa, including growth deficiency, facial dysmorphisms, abnormal hand positioning, hip dislocation, hypotonia and mental retardation. However, this syndrome also normally includes cloudy corneas and the development of 'pseudoathetoid movements' up to age of three (Karnes *et al.*, 1992) but these symptoms were not seen in these patients, because of which we changed the diagnosis to CLGDD after clinical follow-up. A differential diagnosis was also made with other forms of congenital cutis laxa, particularly the recessive type associated with arterial tortuosity, aneurysms and emphysema, Costello syndrome, Ehlers-Danlos syndrome, acrogeria, and the progeroid syndromes, especially the neonatal form of Wiedemann-Rautenstrauch syndrome.

With the recent discussions in the literature involving CLGDD, GO and WSS we reevaluated patients 1 and 2 and found their symptoms to be compatible with these conditions. Assuming that the three terms (CLGDD, GO and WSS) refer to the same condition, 71 patients have been described in the literature to date. *i.e.* 31 as CLGDD, 26 as GO and 14 as WSS. We reviewed the main reports on CLGDD, GO and WSS and have summarized the clinical findings of well-documented patients in Table 2. The common features of all three conditions as well as other relevant findings are discussed below.

Table 1 - Skin measurements (mm) of patients 1 and 2 compared to controls matched for age, sex and skin site.

Individual	Epidermal rete ridges	Suprapapillary epidermal plates	Median dermal thickness
Patient 1	0.09	0.04	0.37
Control 1	0.05	0.02	0.70
Patient 2	0.08	0.03	0.69
Control 2	0.05	0.02	1.10

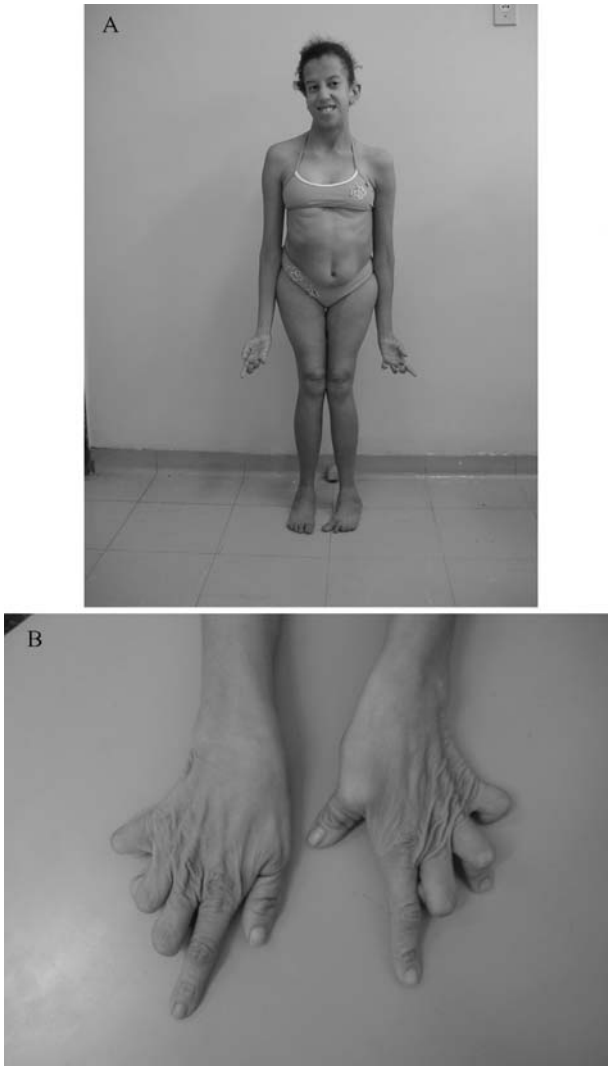

Figure 4 - Patient 2 at 10 years of age. Note the prominent abdomen, genu valgum, lumbar lordosis and prognathism (A) as well as the aged appearance of the dorsum of the hands with abnormal positioning of the fingers (B).

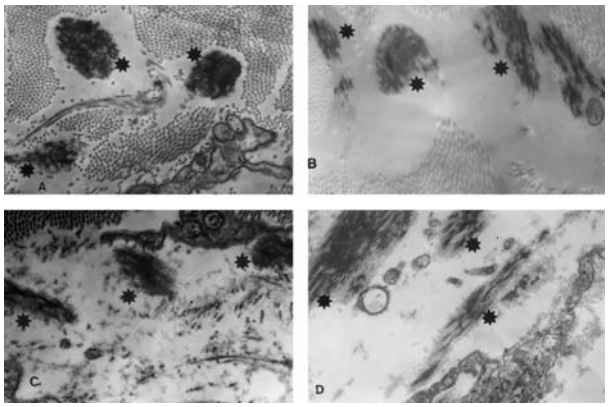

Figure 5 - Skin ultrastructural micrographs taken at an original magnification of x 8,000. (A) Irregular masses of dark elastic tissue in the reticular dermis of buttock skin from patient 1 compared to (B) buttock skin of a normal control individual matched for age and sex; (C) decrease in the amount of elastic fiber in torso skin from patient 2 in comparison with (D) control torso skin from a normal region of a control individual matched for age and sex.

Table 2 - Main clinical features of cutis laxa with growth and developmental delay (CLGDD), Geroderma osteodysplastica (GO) and wrinkly-skin syndrom (WSS) according to descriptions in published papers.

	Gender	IUGR	Postnatal growth def.	Neuro-motor re-tardation	Hypotonia	Senile appear.	Loose skin	Prominent blood vessels	Craniofacial dysmorphisms	Hernia	Hip dislo-cation	Joint laxity
Cutis laxa with growth and development delay												
1 Debré *et al.* (1937)						+	+					+
2 Fittke (1942)	F	+	+	+	+	+	+		+		+	
3 Bittel-Dodrzynska & Siniecki (1964) case 1	F	+	+	+		+	+		+		+	+
4 Bittel-Dodrzynska & Siniecki (1964) case 2	F	+	+	+	+	+	+		+		+	+
5 Bittel-Dodrzynska & Siniecki (1964) case 3	F	+				+	+	+	+		+	+
6 Reisner *et al.* (1971) case 1	F	+	+	-			+	+	+		+	+
7 Reisner *et al.* (1971) case 2	F	+	+	+			+	+	+		+	+
8 Philip (1978)	M	+				+	+	+	+	+	+	+
9 Agha *et al.* (1978) case 2	F	+	-	+	-	+	+		+	+	+	+
10 Sakati *et al.* (1983) case 2	F	+	+	+			+		+		-	
11 Sakati *et al.* (1983) case 3	F		+	-		+	+		+		+	+
12 Sakati *et al.* (1983) case 4	F	-					+				+	+
13 Sakati *et al.* (1983) case 5	F	+					+				+	+
14 Sakati *et al.* (1983) case 6	F		+	+	+		+		+		+	+
15 Fitzsimmons *et al.* (1985) case 1	M	+	+	+	+	+	+		+	+	+	+
16 Fitzsimmons *et al.* (1985) case 2	M				+	-	+		+	+		+
17 Fitzsimmons *et al.* (1985) case 3	M	-	-	-		-	+		+	-		
18 Fitzsimmons *et al.* (1985) case 5	M	-	-	-	+		+		+			
19 Allanson *et al.* (1986)	F	+	+	+	+		+		+		-	+
20 Patton *et al.* (1987) case 1	M	+	+	+			+		+			+
21 Patton *et al.* (1987) case 2	F	+	+	+			+		+		-	+
22 Patton *et al.* (1987) case 3	M			+			+		+			
23 Patton *et al.* (1987) case 4	F						+				+	
24 Patton *et al.* (1987) case 6	M	+	+	+	+		+		+	+		
25 Goldblatt *et al.* (1988)	M	+	+	+			+	+	+	+		+
26 Ogur *et al.(*1990) case 1	M	+	+	+	+	+	+		+	+	-	+
27 Ogur *et al.(*1990) case 2	F	+	+	+			+		+			
28 Imaizumi *et al.* (1994)	M	+	+	+		+	+			+		
39 George *et al.* (1998) case 1	F					+	+		+			
30 George *et al.* (1998) case 2	F					+	+		+			+
31 Karakurt *et al.* (2001)	F		+				+		+	+		-
Subtotal	11:19 [M:F]	19/ 22	18/ 21	17/ 21	9/ 10	13/ 15	31/ 31	5/5	26/ 26	9/ 10	14/ 18	20/ 21
Wrinkly skin syndrome												
32 Gazit *et al.* (1973) case 1	F	+	+	+	+		+	+	-		+	-
33 Gazit *et al.* (1973) case 2	F		+	-	+		+	+	-		-	-
34 Gazit *et al.* (1973) case 3	M			-	-		+	-	-		-	
35 Goodman *et al.* (1982) case 1	F	+	+	+	+		+	+	+		+	
36 Goodman *et al.* (1982) case 2	F	+	-	+	+		+	+	+		+	
37 Karrar *et al.* (1983) case 1	F	+	+	-	-	+	+	+	+		+	
38 Karrar *et al.* (1983) case 2	M	+	+	-	-	+	+	+	+		+	
39 Casamassima *et al.* (1987)	F	+	+	+	+	-	+	+	+		-	+
40 Hurvitz *et al.* (1990)	M		-	-	+	-	+	+	+		+	
41 Kreutz & Wittwer (1993) case 1	M	-	+	+	+	+	+	+	+	+	-	+
42 Kreutz & Wittwer (1993) case	M	-	+	+	+	+	+	+	+	+	-	
43 Kreutz & Wittwer (1993) case 3	F		-	+	-	+	+	+	+		-	
44 Azuri *et al.* (1999)	F	+	+	+	+	-	+	+	+		+	+
45 Boente *et al.* (1999)	F	-		-	+	-	+		-			-
subtotal	5:9 [M:F]	7/10	9/12	8/14	10/14	5/9	14/14	12/13	10/14	2/2	7/13	3/6

Table 2 (cont.)

	Gender	IUGR	Postnatal growth def.	Neuro-motor re-tardation	Hypotonia	Senile appear.	Loose skin	Prominent blood vessels	Craniofacial dysmorphisms	Hernia	Hip dislo-cation	Joint laxity
Gerodermia osteodysplastica												
46 Boreux (1969) case 1	M		+	+	+	+	+	+	+	+	+	+
47 Boreux (1969) case 2	M		-	-		+	+	+	+			+
48 Boreux (1969) case 3	F		-	-		+	+	+	+			+
49 Boreux (1969) case 4	F	?	+	-		+	+					+
50 Boreux (1969) case 5	M	-	+	+			+		-	+	+	+
51 Hunter *et al.* (1978) case 1	M		-	+		+	+	+	+		+	+
52 Hunter *et al.* (1978) case 2	M		-	-		+	+		+		+	+
53 Hunter *et al.* (1978) case 3	F	-	-	-		+	+		+		+	+
54 Hunter *et al.* (1978) case 4	F	-	-			+	+		+		+	+
55 Hunter *et al.* (1978) case 5	M	-	+	+	+	+	+	+	+	+	+	+
56 Hunter *et al.* (1978) case 6	M	-	-	?		+	+		+	+	+	+
57 Lisker *et al.* (1979) case 1	M	+	+	+		+	+		+		+	v
58 Lisker *et al.* (1979) case 2	M		+			+	+		+			
59 Lisker *et al.* (1979) case 3	M		+			+	+		+			
60 Hunter (1989)	F	+	-	+		+	+	+	+			+
61 Lustmann *et al.* (1993) case 1	F	-		-		+	+		+		+	+
62 Lustmann *et al.* (1993) case 2	M	-		-		+	+		+		+	+
63 Eich *et al.* (1996) case 1	F	+	+	-			+			+	+	+
64 Eich *et al.* (1996) case 2	M	-	+	-			+		+	+	+	+
65 Al-Torki *et al.* (1997) case 1	F		-			+	+		+		+	+
66 Al-Torki *et al.* (1997) case 2	F	-	+	+	+	+	+		+		+	+
67 Al-Gazali *et al.* (2001) case 1	F	+	-	?	+	+	+	+	+	-	+	+
68 Al-Gazali *et al.* (2001) case 2	M	-	-	?	-	-	+	+	+	+	-	+
69 Al-Gazali *et al.* (2001) case 3	M	-	-	?	-	-	+	+	+	+	+	+
70 Al-Gazali *et al.* (2001) case 4	M	+	-	+		-	+	+	+	+	-	+
71 Al-Gazali *et al.* (2001) case 5	M	+	+	+		-	+	+	+	+	-	+
Subtotal	16:10	6/ 16	11/ 24	9/ 19	4/6	19/ 23	26/26	11/ 11	23/ 24	10/ 11	17/ 19	24/ 24
Other reports												
72 Khakoo *et al.* (1997) case # 1	M	+		+		+	+		+			+
73 Khakoo *et al.* (1997) case # 2	M	+		+			+		+		+	+
74 present report, case # 1	M	+	+	+	-	+	+	+	+	+	-	-
75 present report, case # 2	F	+	+	+	+	+	+	+	+	-	+	+
Subtotal	3:1	4/4	2/2	4/4	1/2	3/3	4/4	2/2	4/4	1/2	2/3	3/4
Total	35:39	36/ 52	40/ 59	38/ 59	24/ 32	40/ 50	75/75	30/ 31	63/ 68	22/ 25	40/ 53	50/ 55

Key: IUGR = intrauterine growth retardation; M = male; F = female; + = present; - = absent; ? = uncertain; empty cell = unavailable data.
Notes:
1) Case 1 of Agha *et al.* (1978) had type I autosomal recessive cutis laxa. 2) Case 1 of Sakati *et al.* (1983) was the same as case 2 in Agha *et al.* (1978). 3) Cases 5 and 7 of Patton *et al.* (1987) were later re-evaluated and defined as having Costello syndrome (Patton and Baraitser, 1993; Davies and Hughes, 1994). 4) Case 1 of Ogur *et al.* (1990) also appears in Van Maldergem *et al.* (1989). 5) The family described by Bamatter *et al.* (1950) was reviewed several times and a very detailed description of the five affected members was published by Boreux (1969). 6) Lustmann *et al.* (1993) cited other two affected sibs. 7) A male relative of the girls described by Al-Torki *et al.* (1997) was described as having a similar phenotype.

Inheritance and epidemiology

The reports that both male and females are affected by CLGDD, GO and WSS, along with the recurrence of affected individuals in the same sibship with normal parents and the presence of parental consanguinity lead to the conclusion that autosomal recessive inheritance is involved in these conditions. Consanguinity is reported very frequently, occurring in half of the families who have offspring diagnosed with WSS and in at least one third of the families with offspring having CLGDD, while consanguinity was probable in 20% of the families with a history of GO and confirmed in a further 60% (including two patients who were products of sibling incest).

There are no data to establish the precise incidence of CLGDD, GO and WSS but a large number of affected families are of Middle Eastern, especially Muslim, background,

suggesting a higher gene frequency in this population. Consanguinity is common in the Middle East and in some other regions but the low reported frequency of these conditions shows that the disorder is rare.

Growth and development

Although prenatal growth deficiency is almost always present in CLGDD some individuals can reach a normal final height (Sakati *et al.*, 1983). Increased arm span/height ratio and decreased upper/lower body segment has been described in several GO patients and could be caused by vertebral body collapse (Hunter *et al.*, 1978; Al-Torki *et al.*, 1997). Failure to thrive has been described in at least two individuals with GO (Fitzsimmons *et al.*, 1985; Azuri *et al.*, 1999).

Neuropsychomotor development is generally delayed and hypotonia is frequent with poor abdominal muscle tone occurring in some patients. Several adults have been reported as having normal intelligence and the degree of neurological impairment, when present, seems to vary from learning disabilities (Al-Gazali *et al.*, 2001) to severe mental retardation (van Maldergem *et al.*, 1989). Hyperactivity has also been reported in GO patients (Lisker *et al.*, 1979). Febrile seizures are frequent and there is at least one report of a patient with epilepsy (Patton *et al.*, 1987). A patient described by Azuri *et al.* (1999) as having WSS seemed to present mild neurological involution with poor verbal contact after febrile seizures at the age of 27 months. Febrile seizures were also reported in a GO sibship consisting of a girl and her brother who later developed tonic-clonic convulsions and suffered from selective mutism (Al-Gazali *et al.*, 1973).

Puberty in one female patient was described as occurring within the normal range (Al-Gazali *et al.*, 1973), which was also the case for our patient 2. There are no specific data on longevity, but there has been a report of a 47-year-old man with GO (Boreux, 1969).

There is variable inter and intrafamilial expressivity and males described as having CLGDD seem to be more severely affected (Fitzsimmons *et al.*, 1985), especially in the reports of Van Maldergem *et al.* (1989) and Ogur *et al.* (1990). Increased severity in a male was also seen by us in patient 1.

Dermatologic aspects

The most striking characteristics of CLGDD, GO and WSS involve the skin (principally that of the neck, abdomen, hands and feet), which is usually described as loose, lax or wrinkled and which when stretched takes a long time to return to its normal position. Wrinkling is observed in many parts of the body, especially the abdomen when sitting, and there is exacerbation of the palmar and plantar creases. Individuals with these conditions often appear aged even when neonates and this appearance may become accentuated with age, probably related to the sagging cheeks which are sometimes present (Ogur *et al.*, 1990). Drooping and eversion of the lower lip may lead to eclabium and the same may occur with the lower lids leading to ectropion.

The skin heals normally and there is no tendency to easy bruising or bleeding (Casamassima *et al.*, 1987).

Prominent veins may appear on the trunk and limbs of infants but not in older individuals and this has been considered a key feature for differentiating CLGDD and WSS from GO, although Al-Torki *et al.*(1997) reported prominent veins in some families with GO.

Dermatoglyphic studies of these three conditions showed no significant abnormality other than an increased number of palmar and plantar creases, especially in reports of WSS (Gazit *et al.*, 1973; Casamassima *et al.*, 1987; Hurvitz *et al.*, 1990). Many patients exhibit single transverse palmar creases.

Craniofacial abnormalities

Microcephaly is the most frequent cranial abnormality, whereas brachycephaly (Fitke, 1942; Sakati *et al.*, 1983), turricephaly (Allanson *et al.*, 1986) and dolichocephaly (Imaizumi *et al.*, 1994) can occur. Wide open fontanels with delayed closure and widely spaced sutures have been reported in many cases, and frontal bossing, prominent forehead and triangular face have also been described.

Besides an aged appearance, several minor craniofacial dysmorphic signs are present in almost all descriptions, including low-set, dysmorphic and/or large and protruding ears, hypertelorism and telecanthus, epicanthal folds, downslanting palpebral fissures, synophrys, blue sclera, broad and flat nasal bridge, midface hypoplasia, sagging cheeks, prominent nose, long nasolabial philtrum, high arched palate, and prognathism. The latter may become more pronounced with age (Al-Gazali *et al.*, 2001). The malar-maxillary hypoplasia associated with mandibular prognathism can lead to important cosmetic and functional oral problems requiring surgical intervention (Lustmann *et al.*, 1993).

Odontological findings include incomplete primary dentition, discolored and carious teeth (Patton *et al.*, 1987), unerupted molars (George *et al.*, 1998), malocclusion, crossbite, dental crowding and diminished height of the alveolar bone (Lustmann *et al.*, 1993).

Osteoarticular anomalies

Articular laxity is an almost constant finding and may vary from distal phalangeal hyperextensibility to generalized join laxity (Reisner *et al.*, 1971; Sakati *et al.*, 1983; Fitzsimmons *et al.*, 1985).

There have been several reports of unilateral or bilateral congenital hip dislocation and winging of the scapulae is also common. Abnormal positioning of fingers and toes, including adducted thumbs, is frequent (Reisner *et al.*,

1971; Philip, 1978) and was observed in both of our patients.

Other reported osteoarticular features are: a wide space between the first and second toes; talipes equinovarus; metatarsus adductus; genu recurvatum or genu valgum; flat feet; calcaneus valgus; fifth finger clinodactyly; and pectus excavatum. Scoliosis and other spinal deformities may also be present.

A tendency to fractures has been frequently described In GO, probably resulting from osteoporosis which is also thought to cause vertebral collapse and subsequent platyspondyly (Al-Gazali *et al.*, 2001).

Anomalies detected by radiological examination and imaging

Although bone changes are part of the phenotypic spectrum of CLGDD, GO and WSS, radiological evaluation has not been systematically included in all reports, this being especially true for WSS. Persistence of anterior fontanel, Wormian bones and osteoporosis in variable degrees are common findings in CLGDD and GO. Vertebral changes, usually biconcave vertebrae and platyspondyly leading to spinal deformities have been commonly described in GO (Al-Gazali *et al.*, 2001). Bone age delay has been described in CLGDD (Fitzsimmons *et al.*, 1985) but bone age was cited as being normal in the six patients with GO described by Hunter *et al.* (1978).

An enlarged mandibular lingula in the shape of a wide funnel was reported in two sibs with GO by Lustmann *et al.* (1993) who described this as a very unusual finding.

A metaphyseal peg has been described in a sib by Eich *et al.* (1996) who stated that the peg was invisible in infancy and only became apparent at 4 to 5 years of age following physeal closure. These authors also noted brachymesophalangy V on the right hand of the sister sib and a relatively large and cone shaped epiphysis of the distal phalanx on the right thumb of her brother.

Diverticula of the bladder and gastrointestinal tract appear to have been described only in patients with CLGDD, but probably there was no specific search for these features in GO or WSS reports.

Three patients from two families with GO had abnormalities of the corpus callosum. One patient had thinning of the posterior body and beginning of the splenium, possibly representing a normal variant, while the second patient had agenesis of the corpus callosum and small open schizencephaly in the left occipital area and cortical dysplasia in the right occipital area and his brother had absent corpus callosum with slightly enlarged lateral ventricles (Al-Gazali *et al.*, 2001).

Other characteristics

Premature birth and breech presentation have been described in some cases and polyhydramnios was once reported (Fitzsimmons *et al.*, 1985).

Inguinal and/or umbilical herniae are frequent, being particularly prominent in the report on a Turkish boy by Van Maldergem *et al.* (1989) and Ogur *et al.* (1990). Diaphragmatic hernia have also been reported (Fitzsimmons *et al.*, 1985).

Abnormal genitalia, with hypoplastic labia minora and hypoplastic to prominent labia majora have been described in females (Sakati *et al.*, 1983), while in males cryptorchidism is frequent (Hunter *et al.*, 1978) and hydrocele has been reported once (Fitzsimmons *et al.*, 1985).

A few ophthalmologic changes have also been reported, including variable degrees of myopia (Boreux, 1969) as well as esotropia and hypertropia (Sakati *et al.*, 1983).

Cardiologic anomalies include atrial septal defect with an aneurysm of the atrial septum at the fossa ovalis (Casamassima *et al.*, 1987), mild aortic enlargement (Azuri *et al.*, 1999) and mitral valve prolapse (Karakurt *et al.*, 1997).

Hydronephrosis is common in CLGDD and one of the patients described by Khakoo *et al.* (1997) had bladder atonicity that was surgically corrected.

Rare anomalies

There were inconstant reports in the literature of the following anomalies: dystrophic nails (Patton *et al.*, 1987); hypoplastic nipples (Sakati *et al.*, 1983; Ogur *et al.*, 1990); cleft lip (Patton *et al.*, 1987); bilateral coloboma of the macula (George *et al.*, 1998); microcornea; arcus senilis; pseudo epiphyses of the second metacarpal bones (Lisker *et al.*, 1979); and unilateral absence of the pisiform bone (Boreux, 1969).

Saggital and left coronal craniosynostosis were reported in one boy described by Fitzsimmons *et al.* (1985), although these authors remarked that this finding could be coincidental.

In the report of George *et al.* (1998) on two sisters with CLGDD, both presented pulmonary emphysema and one exhibited bilateral sensory neural deafness, which could be coincidental findings due to parental consanguinity.

Kreuz and Wittwer (1993) found a 2q32 interstitial deletion in a mother and two sons described as having WSS, this report being atypical not only in respect to the chromosomal findings but also because there were three affected individuals in two generations which suggests autosomal dominant inheritance. It is unclear whether this family represents a true case of WSS or another condition associated with loose skin.

Histological studies

Most patients were not submitted to histological studies. The findings are very similar in CLGDD, GO and WSS (Hunter *et al.*, 1978; Sakati *et al.*, 1983; Eich *et al.*, 1986; Boente *et al.*, 1999). Optic microscopy using various stain-

ing techniques indicate that in these conditions there is a decreased amount, or almost the complete absence, of elastic fibers as well as heterogeneity in their structure and distribution pattern. The elastic fibers have been reported as exhibiting degenerative changes, with some fibers being fragmented while others were short or clumped or thinner than normal. In the studies in which electron microscopy has been used this technique has shown that there is a considerable reduction of the electron-dense matrices usually seen in the central portions of the elastic fibers (Sakati *et al*., 1983). Normal collagen fibrils have also been reported (Hunter, 1988).

Reports on other designations

Besides the reports citing CLGDD, GO or WSS as proposed diagnosis at least three other patients presenting these features but described under other designations were found in our literature survey.

The patients reported by Khakoo *et al.* (1997) presented pre and post-natal growth deficiency, delayed neuromotor development, generalized lax and wrinkled skin, prominent veins, joint laxity, hip dislocation, herniae, osteoporosis and Wormian bones. One of them had consanguineous parents of Pakistani Muslim origin. Although Khakoo *et al.* (1997) considered these patients as having a distinct form of cutis laxa we feel that it is more probable that they represent additional cases of CLGDD, GO or WSS.

Acrogeria (OMIM 201200) is defined as a condition in which the hands and feet appear prematurely aged, Greally *et al.* (1992) having reported a patient with features of acrogeria as well as additional findings suggesting a progeroid condition and proposed the term acrometageria. Their patient, however, presented pre- and post-natal growth deficiency, congenital skin redundancy, wrinkled skin on hands and feet, prominent scalp veins, microcephaly, aged appearance, bilateral inguinal herniae, brittle teeth, recurrent febrile seizures, joint hyperextensibility, scoliosis and Wormian bones. The clinical picture involves several features of CLGDD, GO and WSS but this patient also showed unilateral anterior polar cataract and electron microscopy of a skin biopsy showed that the skin was normal, although the authors did note that the skin sample was taken from a clinically unaffected area.

Conclusions

Considering all the issues covered in our review of the published literature on CLGDD, GO and WSS we conclude that these conditions share many similarities which suggest that they are the same condition and that this condition follows an autosomal recessive inheritance pattern and has a high frequency in Middle Eastern populations. The main clinical symptoms are loose, wrinkled and thin skin with an aged appearance, joint laxity, variable degrees of growth deficiency, developmental delay and minor craniofacial dysmorphisms. Radiological features include generalized osteoporosis, Wormian bones, vertebral anomalies and probable metaphyseal peg in infancy.

Some characteristics such as the normal intellectual development, tendency to fractures and disproportion of body segments reported in GO or the bladder and gastrointestinal diverticula observed in CLGDD patients can be interpreted as (a) variable expressivity of the disorder, (b) a bias of authorial description or simply (c) the absence of a specific search for these features. Individuals presenting the combination of symptoms described above should be submitted to detailed clinical, radiological and histological evaluation. Final diagnosis should not be confirmed in infancy and clinical information, periodic reevaluation and radiological assessment must be carefully made in order to prevent misdiagnosis.

This puzzling phenotype will remain as a unique but unclear clinical entity until the discovery of its molecular basis, at which time it may well be possible to establish a definitive designation.

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