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Are parents of children with Cockayne syndrome manifesting features of the disorder?

Case reports

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Abstract

Rationale: Postnatal growth failure and progressive neurologic dysfunction and increasing multiorgan involvement are the main clinical features of Cockayne syndrome (CS). CS is a rare autosomal recessive disorder of the group of DNA repair diseases. Usually, genetic carriers, such as parents of patients, are not at risk for developing the disease.

Patient concerns: A series of 14 family subjects (6 children with age range from 6 months to 4 years with CS) and 9 parents (aged from 23 to 34 years) from consanguineous families is reported.

Diagnoses: Ultraviolet irradiation studies were performed on these children and were indicative of CS.

Interventions: Cells of skin fibroblast from these children with the disease showed a symmetrical accumulation of chromosomal aberrations and the nuclear lamina aberrations. Our results showed a significant and simultaneous increase of percent of blebbs and invaginations of the nuclear lamina in all cases CS. The pronounced changes in 12.6 times at atypical form (girl); in 8.5 times at severe form (boy) and in 5.6 times at light form (boy). Percentage of metaphases with chromosomal aberration is significantly higher in CS cells: in 4 times at atypical form, in 3 times at hard form, and in 2 times at light form. The parents of these families (consanguineous families) were intellectually variable between normal/borderline intelligence, though most manifested a constellation of skeletal and extraskeletal abnormalities and notably, the characteristic cachectic facial appearance. The parents were considered as manifesting the mild type of CS, because they showed no abnormalities of DNA repair.

Outcomes: Clinical manifestations in heterozygote carriers of an autosomal recessive disorders is a rare phenomenon as carriers are usually healthy.

Lessons: The interesting finding of the families studied is that there appeared to be a multitude of carriers manifesting with normal to borderline intelligence but with a wide spectrum of skeletal and extraskeletal abnormalities.

Abbreviations: COFS = cerebro-oculo-facio-skeletal syndrome, CS = Cockayne syndrome, ERCC6 = Excision Repair Cross-Complementation Group 6, tc-NER = transcription-coupled nucleotide excision repair, UV = ultraviolet.

Keywords: Cockayne syndrome, heterozygote carrier, radiographs, symptomatic carriers

1. Introduction

Cockayne syndrome (CS) is a rare autosomal recessive disorder and in its classical form, it is a progressive neurological disorder characterized in infancy by sun-sensitivity, resulting in bullae and desquamation of the skin. The characteristic facial appearance does not develop until between the 2nd and 4th years of life when there is a loss of subcutaneous tissue around the eyes, giving the appearance of sunken eyes, as seen in premature ageing.[1] Dermal photosensitivity is often considered a key feature of the diagnosis, particularly after defects in transcription-coupled nucleotide excision repair (tc-NER) were identified in classically affected patients.[2]

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Given that all investigations and interventions in this report were performed as part of the regular health care whose informed consent was obtained on admission, an ethical approval was obtained.

Authors contribution: AAK, MK, NP, VK, NMN, FG, RG and SGK contributed in patients documentation and writing the MS, analysis of data and all approved the final version.

The authors declare no conflicts of interest.

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The CS type I is the classic form with normal intrauterine growth and uneventful birth. However, during the first 2 years of life, disease develops with restricted growth, weight, head circumference, and continuously impairment of central and peripheral nervous system function, vision, and hearing loss. Many patients develop dental caries and photosensitivity.

CS type II is a more severe form with early-onset form of the disease even at birth. The patients develop cataracts or other eye anomalies, arthrogryposis, and contractures of the joints and spine with kyphosis and scoliosis. This type of CS is akin to cerebro-oculo-facio-skeletal (COFS) syndrome and a less defined type CS III, a mild form of xeroderma pigmentosum-Cockayne syndrome (XP-CS).[3]

Some cases have a milder phenotype without abnormalities of DNA repair and distinctive skeletal abnormalities have been described in CS patients.[4] There may also be a later-onset form with normal intelligence and relatively normal growth.[5,6]

Chromosome breakage is seen on exposure of cells to ultraviolet (UV) light. Unlike in xeroderma pigmentosum, excision repair after UV damage is normal, but there is a slow recovery of DNA and RNA synthesis. Any excision repair defects seem to be restricted to actively transcribed genes.[7]

The genetic investigation of CS in our patients and family members has been performed by chromosomal breakage seen on exposure of cells to UV light. It is pointed out, that none of the patients underwent the molecular tests of the genes (*ERCC6* gene for CS type B in about two-third of the patients or *ERCC8* gene for CS type A in one-third of the patients).

2. Materials, methods, and patients

In this study we collected 14 patients (6 children with age range of 6 months to 10 years) with CS and 8 parents (aged from 23 to 34 years) from consanguineous families. Age of diagnosis of CS was around 6 months to 2 years and in correlation with the clinical diagnosis of CS. Signed consents were obtained from the guardians. The study protocol was approved by the Medical Committee of the Paediatric Orthopedic Institute n.a. H. Turner, Department of Foot and Ankle Surgery, Neuroorthopaedics and Systemic Disorders, Pushkin, Saint-Petersburg, Russia) and international collaboration with clinicians and scientists from Paediatric Orthopaedics, Children Hospital, Tunis and with Institute of Cytology RAS, Department of Radiation and Cytology, Saint-Petersburg, Russia. Children with the clinical diagnosis of CS were confirmed via the impaired recovery of RNA synthesis in fibroblasts following UV irradiation.

3. Patients

3.1. Group 1

Patients with early-onset CS: This group of patient included 6 children (4 males and 2 females with age range from 6 months to 4 years). They showed striking failure of growth and marked developmental deterioration around the age of 6 to 12 months. Dwarfism, microcephaly, and mental retardation, a characteristic cachectic facial appearance associated with prominent nose and chin, large eyes, and sunken eyes. Photosensivity was noted in all children of this group. Early deafness, cataracts, later pigmentary degeneration, and progressive neurological deterioration occurred and were associated with pyramidal, cerebellar and in 1 patient extrapyramidal dysfunction. Clinical phenotypes showed a 6-month-old boy was seen at the age of 7 days, referred to the Department of Pediatric Orthopaedics because of congenital dislocation of the hips, and congenital contractures at the knees, elbows, and ankles. In the letter of referral the diagnosis was that of suspected cerebral palsy. One of the cousins presented with a hypertonic cerebral palsy-like picture, whereas the other was floppy with multiple joint contractures and a unilateral cataract. The child was born, full term, and the birth weight, head circumference, and length were all around the 10th percentile. Examination revealed multiple congenital contractures, and marked hypertonicity in all 4 limbs. The craniofacial examination showed sunken eyes due to loss or periorbital fat. The hands were small, and there was congenital dislocation of the hips, congenital scoliosis and pes cavus (Fig. 1A). A

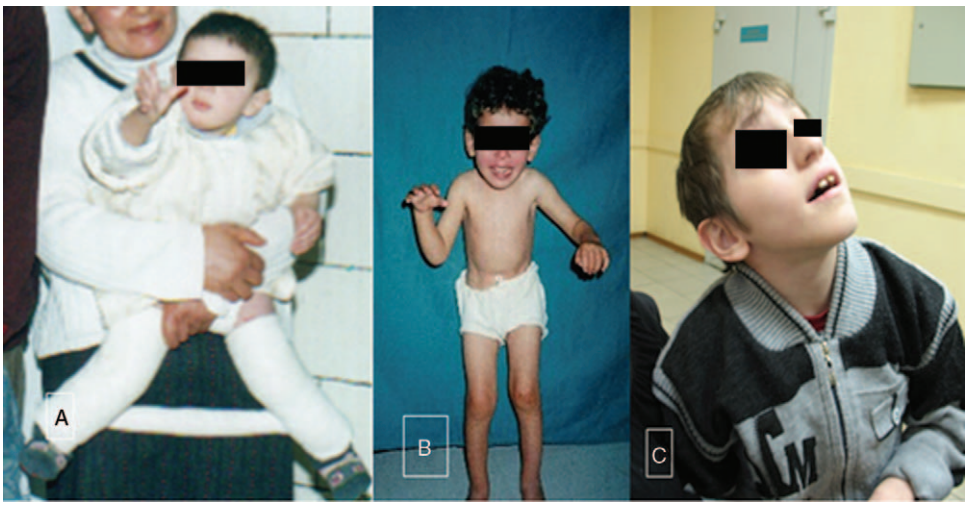

Figure 1. (A) showed a 6-month-old boy was seen at the age of 7 days, referred to the Department of Pediatric Orthopaedics because of congenital dislocation of the hips, and congenital contractures at the knees, elbows, and ankles. In the letter of referral, the diagnosis was that of suspected cerebral palsy. (B) A female patient was referred to the Department of Pediatric Orthopaedics at the age of 7 years because of congenital dislocation of the hips, and congenital contractures at the knees, elbows, and ankles. Examination revealed, severe growth deficiency (-4SD), microcephaly, and progressive neurological disorder. Moreover, since infancy she manifested sun-sensitivity, resulting in bullae and desquamation of the skin. Multiple congenital contractures and marked hypertonicity in all 4 limbs. The craniofacial examination showed sunken eyes due to loss or periorbital fat. (C) A female patient was seen at 13 years of age in the Pediatric Academy. She has severe early-onset form CS with progressive neurological disorder, underweight, inability to walk and talk. Her cousin of 6 years old had a mild form of CS without seriously neurological pathologies and his ability to move was not broken. Cousins did not show the UV sensitivity. CS = Cockayne syndrome, UV = ultraviolet.

female patient was referred to the Department of Pediatric Orthopaedics at the age of 7 years because of congenital dislocation of the hips, and congenital contractures at the knees, elbows, and ankles. Examination revealed, severe growth deficiency (-4SD), microcephaly, progressive neurological disorder. Moreover, since infancy she manifested sun-sensitivity, resulting in bullae and desquamation of the skin. Multiple congenital contractures and marked hypertonicity in all 4 limbs. The Craniofacial examination showed sunken eyes due to loss or periorbital fat (Fig. 1B). A female patient was seen at 13 years of age in the Pediatric Academy. He has severe early-onset form CS with progressive neurological disorder, underweight, inability to walk and talk. His cousin of 6 years old had a mild form of CS without seriously neurological pathologies and his locomotor system was acceptable. Cousins did not show the UV sensitivity (Fig. 1C)

3.1.1. Immunofluorescence staining and microscopy analysis. The cell lines from these children were staining at primary antibodies to mouse immunglobulin G (IgG) against the nuclear protein *LMNA* A/C (Abcam) diluted 1:100. Goat IgG against mouse and rabbit IgG conjugated with FITC at a dilution of 1:500 (Sigma Aldrich) were used as secondary antibodies. Cells incubated only with secondary antibodies were used as control of the specificity of the immune reaction. To prevent rapid "burning out" of the fluorescent label, anti-fading with DAPI (4′,6-diamidino-2-phenylindole) (Invitrogen) was used.

Microscopy and image analysis were carried out using a Zeiss LSM 5 PASCAL laser scanning confocal microscope. For visualization of fluorophores, argon (488 nm) and helium neon (543 nm) lasers were used. To obtain images, the scanning module of a microscope was used with the aid of computer and the corresponding LSM 5 PASCAL software. For analysis of the obtained images (determination of the level of intensity of fluorescence), the LSM 5 PASCAL and WCIF ImageJ 1.37 m software was applied accordingly.

3.2. Group 2

Eight parents were included: 4 fathers and 4 mothers, with age range from 23 to 34 years. Interestingly, they manifested a wide spectrum of abnormalities: facial features with loss of subcutaneous fat. Loss of intraorbital fat, giving a sunken-eyed appearance. Their wizened appearance and cachectic facial appearance with resemblance of little old men and women were notable features. Father aged 27 years: manifested early aging, pigmentary retinopathy, hearing loss, progressive sclerosis of the skull base and the calvarium and early degenerative changes of the lumbar spine with subsequent L4/5 prolapsed disc (Fig. 2). A 34 year-old father and his 5-year-old daughter with confirmed CS (Fig. 3). The father showed relevant clinical features of wizened appearance and cachectic facial appearance. He manifested hearing loss, border-line intelligence, thoracic kyphosis and overwhelming sclerosis of the skull base and the calvarium (Fig. 4). Three mothers had had a history of multiple spontaneous abortions, and still-births. Gestations have been described of being difficult, and some mothers had experienced frequent bouts of heavy bleeding amid the first/second trimesters. The mother's average heights ranged between 146 and 153 cm. Surprisingly, most of the parents have a history of early degeneration over the lumbar spine and the weight bearing zones. Four out of 8 parents manifested progressive ossification of the skull base. Skull radiographs have been performed for several patients (children and adults). Lateral skull radiograph of a 5-year-old girl showed

Figure 2. A 27-year old father manifested early aging, pigmentary retinopathy, hearing loss, progressive sclerosis of the skull base and the calvarium, and early degenerative changes of the lumbar spine with subsequent L4/5 prolapsed disc.

hyperostosis of the skull base and the calvarium (Fig. 4A). Lateral skull radiograph of a 34 year-old father showed diffuse skull base sclerosis, J-shaped sella turcica overwhelmed by immense hyperostosis of the cranium (Fig. 4B). Lateral skull radiograph of the spouse of Figure 3 showed calvarial thickening, similar but less sclerosis of the skull base and all patients showed wormian bones of the occipital areas with variable intensity. All patients showed J-shaped sella turcica (Fig. 4C) and lateral skull radiograph of a 13-year-old-girl showed sclerosis of the calvaria and hyperostosis of the skull base. All patients (children and adults) showed calvarial sclerosis, hyperostosis of the skull base, wormian bones and J-shaped sella turcica (Fig. 4D).

4. Results

4.1. Laboratory findings

The main changes of the nuclear lamina are invaginations, blebs and thinning of the nuclear lamina layer, forming characteristic rims. The most severe pathological changes in the nuclear lamina are the simultaneous presence of both blebs and invaginations. We very thoroughly approached the analysis of the nuclear lamina and identified several groups of changes in the lamina. We

Figure 3. A 34-year-old father and his 5-year-old daughter with confirmed CS. The father showed relevant clinical features of wizened appearance and cachectic facial appearance. He manifested hearing loss, border-line intelligence, thoracic kyphosis, and overwhelming sclerosis of the skull base and the calvarium. CS = Cockayne syndrome.

identified 3 main groups: the norm, pronounced changes, and the beginning of changes. In the last 2 groups, we identified the same subgroups: blebs, invaginations, and blebs + invaginations. The group with pronounced changes contained the item "defragmentation." This approach allowed us to study the change in the nuclear lamina thoroughly.

Thus, we have displayed that there is a correlation between the severity of the disease and the allotment of the most severe pathological changes of lamina. We also established a correlation between the percentage of changes in the nuclear lamina and chromosome aberrations.

Our results showed a significant and simultaneous increase of percent of blebbs and invaginations of the nuclear lamina in all cases CS. The pronounced changes in 12.6 times at atypical form (girl); in 8.5 times at severe form (boy), and in 5.6 times at light form (boy). Percentage of metaphases with chromosomal aberration is significantly higher in the CS cells: in 4 times at atypical form, in 3 times at hard form, and in 2 times at light form (Table 1).

Interestingly, these results showed a symmetrical increase of percentage of nuclear and chromosomal aberrations in all cell lines. This fact allows us to assume that the emergence of chromosomal aberrations can be correlated with the accumulation of aberrations nuclear lamina. The nuclear lamina performs an important function in the life of the cell: it participates in both nucleus and cytoskeleton, mechanical stability, chromatin organization, signaling, gene regulation, genome stability, and cell differentiation. We can suggest that the changes in nuclear lamina can lead to chromosomal aberrations. In other words, some mutations in CS genes perhaps can lead to aberrant nuclear lamina structure. Karyotype analyses of the cell lines were carried out using cells with no more than 10 culture passages. These cells were processed using standard cytogenetic techniques. Basically, cells were treated with 0.06 μg/mL of Colcemid (Gibco) for 10 hours at 37°C, trypsinized, treated with 0.075 M hypotonic KCl solution, and fixed with Carnoy fixative. Cells were then dropped on a microscope glass slide and dried. Metaphase cells were marked by Giemsa stain. The parents were considered as manifesting the mild type of CS, because they showed no abnormalities of DNA repair (Fig. 5A and B).

5. Discussion

CS is a premature aging disorder characterized by different developmental defects, primary of which are multisystem progressive degeneration and sensitivity to ultraviolet light. Two primary complementation groups of CS have been identified, CSA and CSB proteins presumably functioning in DNA repair and transcription. CSB recruitment is influenced by the type of DNA damage and is most rapid and robust. Inhibition of histone deacetylation altered the dynamics of CSB assembly, suggesting a role for chromatin status in the response to DNA damage.[13,14]

Nuclear lamina is rarely explored in this disease. Although at laminopathies, which is also characterized by muscular and

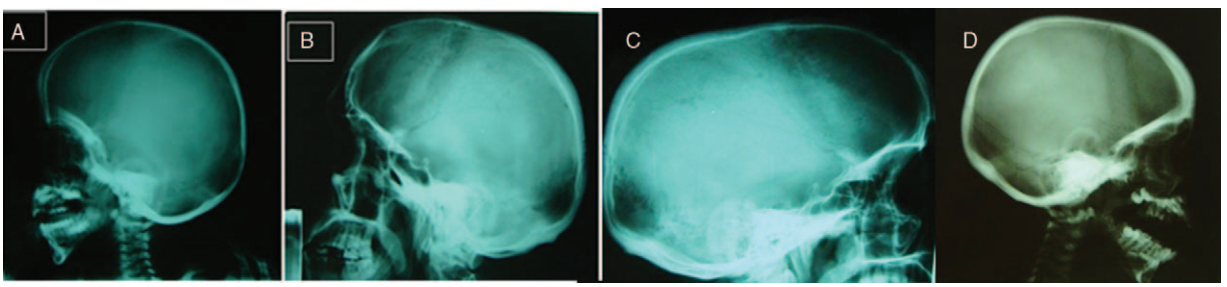

Figure 4. (A) lateral skull radiograph of a 5-year-old girl showed hyperostosis of the skull base and the calvarium. (B) Lateral skull radiograph of a 34-year-old father showed diffuse skull base sclerosis, J-shaped sella turcica overwhelmed by immense hyperostosis of the cranium. (C) Lateral skull radiograph of the spouse of Figure 3 showed calvarium thickening, similar but less sclerosis of the skull base and all patients showed wormian bones of the occipital areas with variable intensity. All patients showed J-shaped sella turcica. (D) Lateral skull radiograph of a 13-year-old girl showed sclerosis of the calvaria and hyperostosis of the skull base. All patients (children and adults) showed calvarial sclerosis, hyperostosis of the skull base, wormian bones, and J-shaped sella turcica.

Table 1

Showed a significant and simultaneous increase of percent of blebbs and invaginations of the nuclear lamina in all cases Cockayne syndrome.

		Developed features				Beginning features			
	Norma	Inv	Blebb	Inv + blebb	Defragme-ntation	Inv	Blebb	Inv+blebb	Chromosomal aberrations
Severe form (girl) 8 years	71.8	1.7	1.3	12.6	1.8	1.5	0.9	8.4	7.7
Severe form (boy) 13 years	73.6	1.5	3	8.5	1.6	3.6	0.9	7.3	5.7
mild form (boy) 7 years	72	0.8	0.8	5.6	1.5	5.1	7.2	7	4
Health donor 10 years	88.8	1.3	2.6			4		3.3	2

skeletal dystrophy, reduction of subcutaneous adipose tissue, optic atrophy, disturbances in DNA repair and signs of accelerated aging, irregularities in the organization of the nuclear lamina studied widely. In our study, we examined and analyzed the aberrations of the nuclear lamina and chromosomes in skin fibroblasts of patients with 3 different forms of CS (severe, atypical, and severe and light).[8,9]

Multiprotein complexes involved in cell development can regulate gene activity at various stages of the transcription process. Results of many works show the important role of nuclear positioning in the control of gene expression where nuclear envelope components play a central role. Active genes localize to nuclear-pore structures on the inner face of the nuclear envelope whereas silent chromatin localizes to non-pore sites. Main function of nuclear-pore components is not only recruiting the RNA-processing and RNA-export but also regulation of transcription level. This capacity might enhance gene expression in a heritable manner.[10]

CS has been considered a progeria, and many of the clinical features resemble accelerated aging. As such, the study of CS affords an opportunity to better understand the underlying mechanisms of aging. The molecular basis of CS has traditionally been ascribed to defects in transcription and transcription-coupled nucleotide excision repair (TC-NER). However, recent work suggests that defects in base excision DNA repair and mitochondrial functions may also play key roles. This opens up the possibility for molecular interventions in CS, and by extrapolation, possibly in aging.[11] The accelerated aging disorder CS has been characterized by progressive brain atrophy, leukodystrophy, cachexia, and growth retardation.[12]

Scheibye-Knudsen et al proposed that patients with Cockayne CS-related DNA repair deficiency that decreased DNA repair would lead to increased PARP1 and perhaps ATM activation because of accumulated DNA damage. Activation of these pathways will lead to decreased NAD+ levels and increased ATP consumption. Increased ATP consumption could explain the cachectic phenotype in the CS patients and the increased metabolism in Csbm/m mice, and increased ATP consumption was indeed found in CSB-deficient cells.[13]

Heterozygote manifestation in recessive disorders is a rare phenomenon and carriers are usually healthy and without disease symptoms. In these families there seems to be a multitude of manifesting carriers. Although the reason for this is not clear, it must be considered in assessing their children suffering from CS. On the other hand, the parents also illustrate the variability of genetic caused conditions despite their biochemical assays were negative. It is well known that partial manifestations of disorders are more common in dominant inheritance where the locus on the unaffected chromosome seems to influence expression, but it is rarer in recessive inheritance where both loci are involved. Whether other (modifying) genes on the same or a different chromosome affects expression and therefore clinical presentation, or whether environmental effects are involved, remains unclear. In our current article, we described 3 children with the clinical diagnosis of CS were confirmed via the impaired recovery of RNA synthesis in fibroblasts following UV irradiation. Other 3 children and their parents were also included because they manifested clear clinical and radiographic phenotypes of CS. The nuclear lamina and karyotype were studied in dermal fibroblasts from 3 patients. Cells of skin fibroblast from 3 children with the

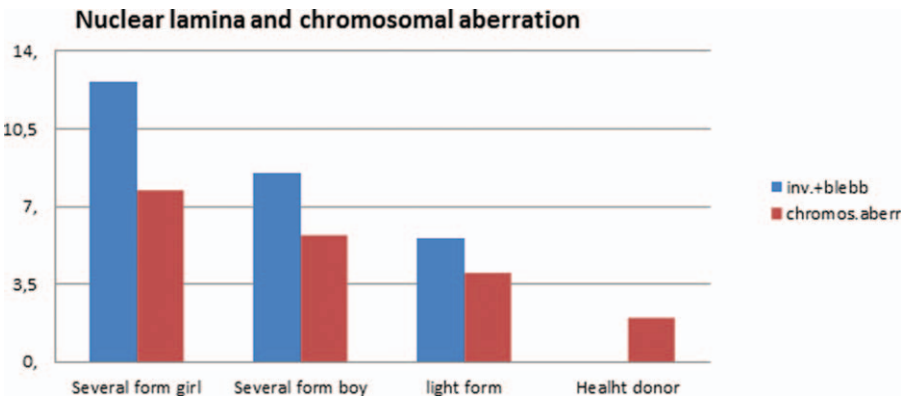

Figure 5. (A) Karyotype analyses of the cell lines were carried out using cells with no >10 culture passages. These cells were processed using standard cytogenetic techniques. Briefly, cells were treated with 0.06 μg/mL of Colcemid (Gibco) for 10 hours at 37°C, trypsinized, treated with 0.075 M hypotonic KCl solution, and fixed with Carnoy fixative. Cells were then dropped on a microscope glass slide and dried. Metaphase cells were marked by Giemsa stain. (B) Showed aberrations of the nuclear lamina in children with CS. CS = Cockayne syndrome.

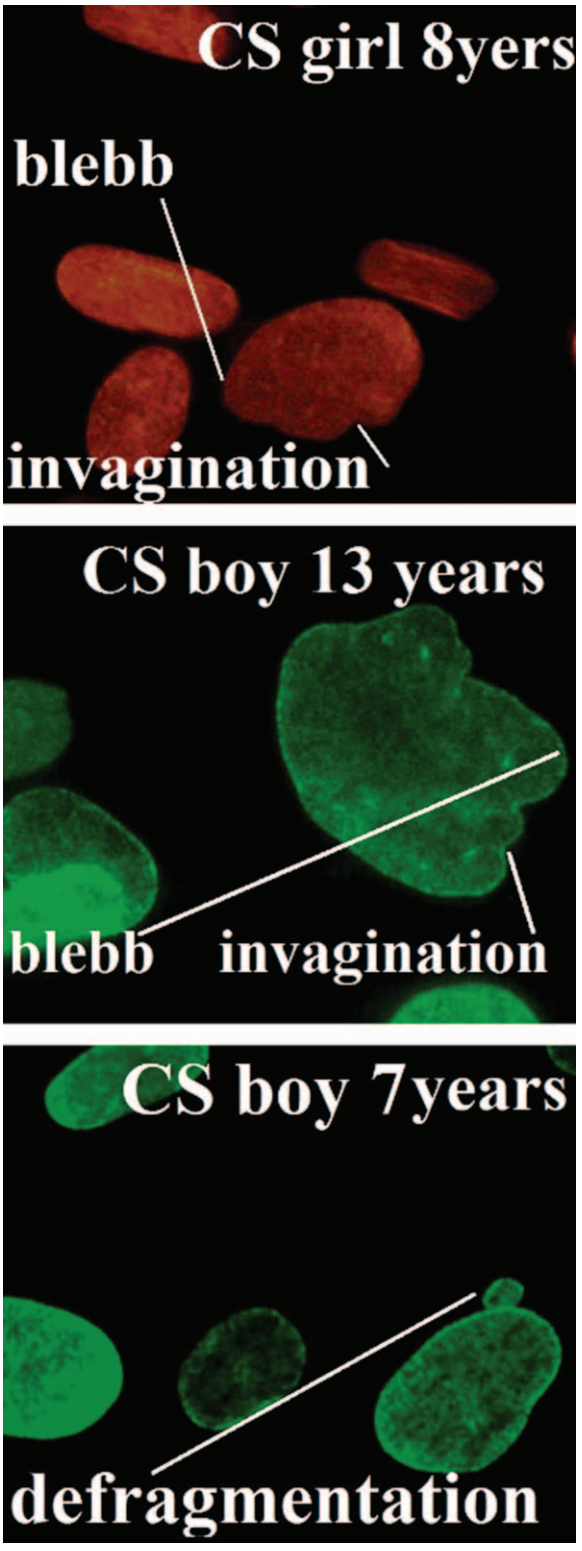

Figure 5. Continued

disease showed a symmetrical accumulation of chromosomal aberrations and the nuclear lamina aberrations.[14–16]

The differential diagnosis of CS should be performed by comparing other disorders such as progeria and other syndromes with premature aging or patients with progeroid phenotype.[17] Bloom syndrome, xeroderma pigmentosum, and other diseases that are characterized by photosensivity are to be considered.[18,19] Also the phenotype of CS overlaps with COFS.[20] CAMFAK (Cataract, Microcephaly, Failure to thrive, Kyphoscoliosis) is a syndromic entity with a phenotype resembling CS.[21]

6. Summary

Interestingly is that intervening members appear to be affected. Parents of the index cases have deficient facial fat and seem prematurely aged with variable manifestations of photosensitivity and telangiectasia. All parents' experienced skeletal abnormalities at certain age of life emerged in connection with severe early degenerative processes along the spine and the weight bearing zones. We noticed that 4 out of 8 parents manifested progressive ossification of the skull base; this sort of abnormality might explain the reason behind the development of visual and hearing problems (myopia, retinopathy, and hearing loss). The progressive sclerosis might play role in diminution and obliteration of the cranial foramina.

The condition in these families has been proven to be CS by specialized tests (chromosome breakage was seen on exposure of cells to UV light). The extreme variation of the clinical phenotype of the severely affected subjects and parents as genetic carriers can explain the variability of the clinical and the cytological criteria of the disorder among the affected children in the same families. Nevertheless, the only constant common features in these families were the clinical phenotype and to certain extent the radiological findings; moreover, looking at the clinical picture of the face, the sunken eyes especially, these occur very rarely in other conditions and together with the natural clinical histories of the parents, the recognition of parents is compelling. It seems highly likely that the changes in nuclear lamina can leads to chromosomal aberrations. Furthermore, we might presume that some mutations in CS-genes perhaps can lead to abnormalities in the nuclear lamina structure.

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