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DeSANCTIS - CACCHIONE SYNDROME*

*Hülya Günöz MD**, *Jak Özsarfati MD****, *Olcay Neyzi MD*****

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DeSanctis-Cacchione syndrome is a rare genetic disorder considered to be a variant of xeroderma pigmentosum. In addition to freckle-like skin lesions, microcephaly, mental deficiency, choreoathetosis, cerebellar ataxia, spasticity, sensorineural deafness, stunted growth and retarded sexual development have been listed as the outstanding features of the syndrome[1]. Hypogonadism has been encountered in a significant proportion of the cases. Death usually occurs at an early age as a result of development of malignancy in the skin lesions.

This report presents the findings in a case of DeSanctis-Cacchione syndrome showing marked growth retardation associated with relatively early pubertal development.

Case Report

D.S., a 14 $\frac{8}{12}$ - year-old girl, was brought to the Istanbul University Endocrinology Clinic with complaints of pigmented areas on her skin, defective hearing and growth failure. The skin lesions had first been noticed at 3 months of age following exposure to sunlight. The lesions had increased progressively with age and showed seasonal fluctuations. Deafness had been noticed only recently. The patient had always been comparatively small in size and retarded in skills. Because she was small for her age and considered to be retarded, the child had not been sent to school at 6 years of age, and had been taught by her mother to read and write. Budding of the breasts had commenced at 8 years of age and menarche at 10, and menstrual periods had occurred regularly since then.

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* From the Istanbul University Faculty of Medicine, Istanbul.
** Associate Professor of Pediatrics, Growth and Development, Department of Pediatrics, Pediatric Endocrinology Unit, Istanbul University Faculty of Medicine.
*** Resident in Pediatrics, Department of Pediatrics, Istanbul University Faculty of Medicine.
**** Professor of Pediatrics, Growth and Development, Department of Pediatrics, Pediatric Endocrinology Unit, Istanbul University Faculty of Medicine.

The patient was the offspring of unrelated healthy parents and had been born at term with a birthweight of 3000 gm following an uneventful pregnancy and delivery to a gravida II, para I mother. The older sibling was a 16-year-old healthy male. There was no history of a similar condition in the immediate or distant relatives of the family.

Physical examination. The patient was found to be a subdued deaf child. In spite of an extensive hearing defect, communication could be established. Her height was 126 cm (height age: 8 years); weight was 23.5 kg (weight age: 7.5 years) [2]. Head circumference was 47.5 cm. Pubertal development was scored as B_3, PH_4 and Ax_3 by the Tanner standards[3,4]. There were numerous café au lait and darker colored spots on the skin all over the body. The majority of these lesions were freckle-like, but larger spots were also present (Figure 1). Choreiform movements of a mild degree occurred occasionally. No other noteworthy physical findings were observed.

Laboratory findings. Evaluation of the x-rays of the hands and wrists showed complete closure of the epiphyses. The sella turcica was evaluated as hypoplastic. The long bones were normal.

Ophthalmologic examination revealed bilateral small bulbi, a nephelion on the right cornea, a nevus on the left conjunctiva and dyspigmented areas in both fundi. A bilateral sensorineural type hearing defect was determined with audiometry.

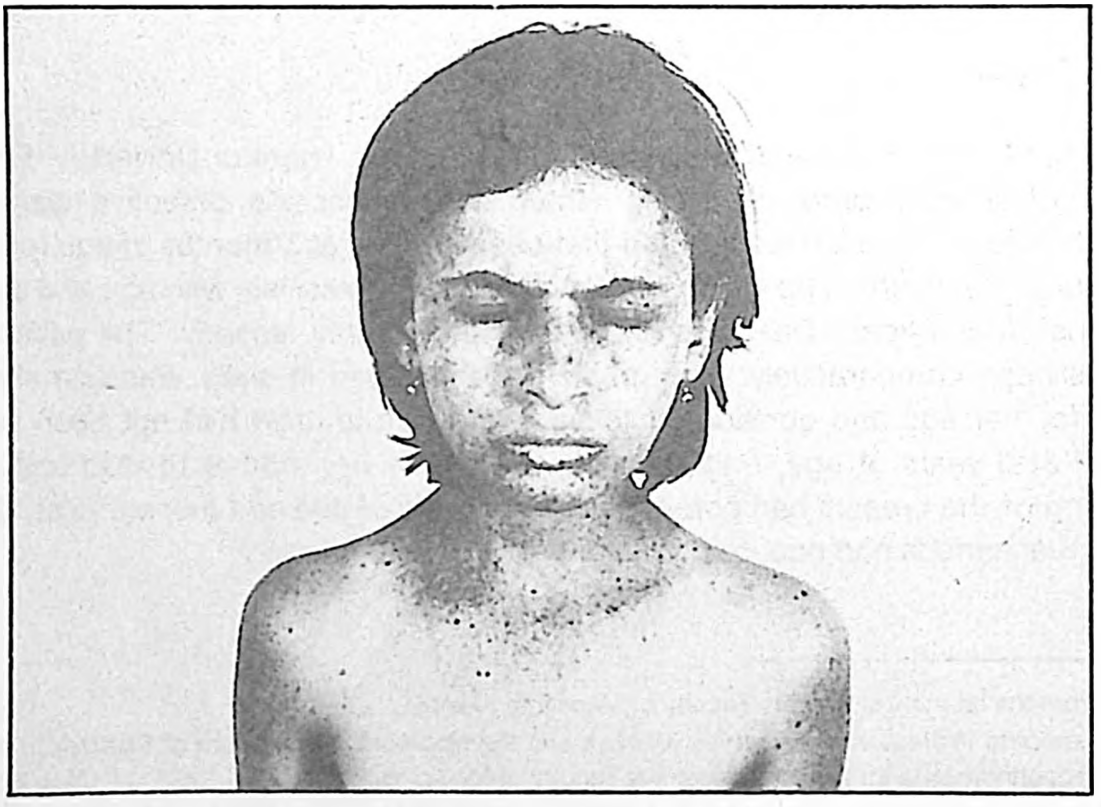

Figure 1.

Appearance of the patient.

Results of I.Q. ratings were 39% on the Stanford-Binet, 45% on the Wechsler Intelligence Scale for Children (WISC) and 53% on the Goodenough tests. However, since the child was able to communicate with relative ease and could read and write, it was concluded that the hearing defect had influenced the tests and that her intelligence level was actually higher than the tests had indicated. Her electroencephalogram was normal.

Skin biopsy displayed atrophy and pigmentation of the basal epithelium, findings which corresponded to the second stage in xeroderma pigmentosum. Electron microscopic findings revealed pigmentation in the basal epithelium and loss of normal structure in the desmosomes between the epithelial cells (Figure 2). Routine hematological evaluation showed moderate iron deficiency anemia. Results of an intravenous glucose tolerance test were normal. Routine blood biochemistry and electrolyte values were within normal ranges. Urine analysis was normal. Urinary uroporphyrin and coproporphyrin concentrations were within normal values (4.8 μg/24 hours and 6 μg/24 hours).

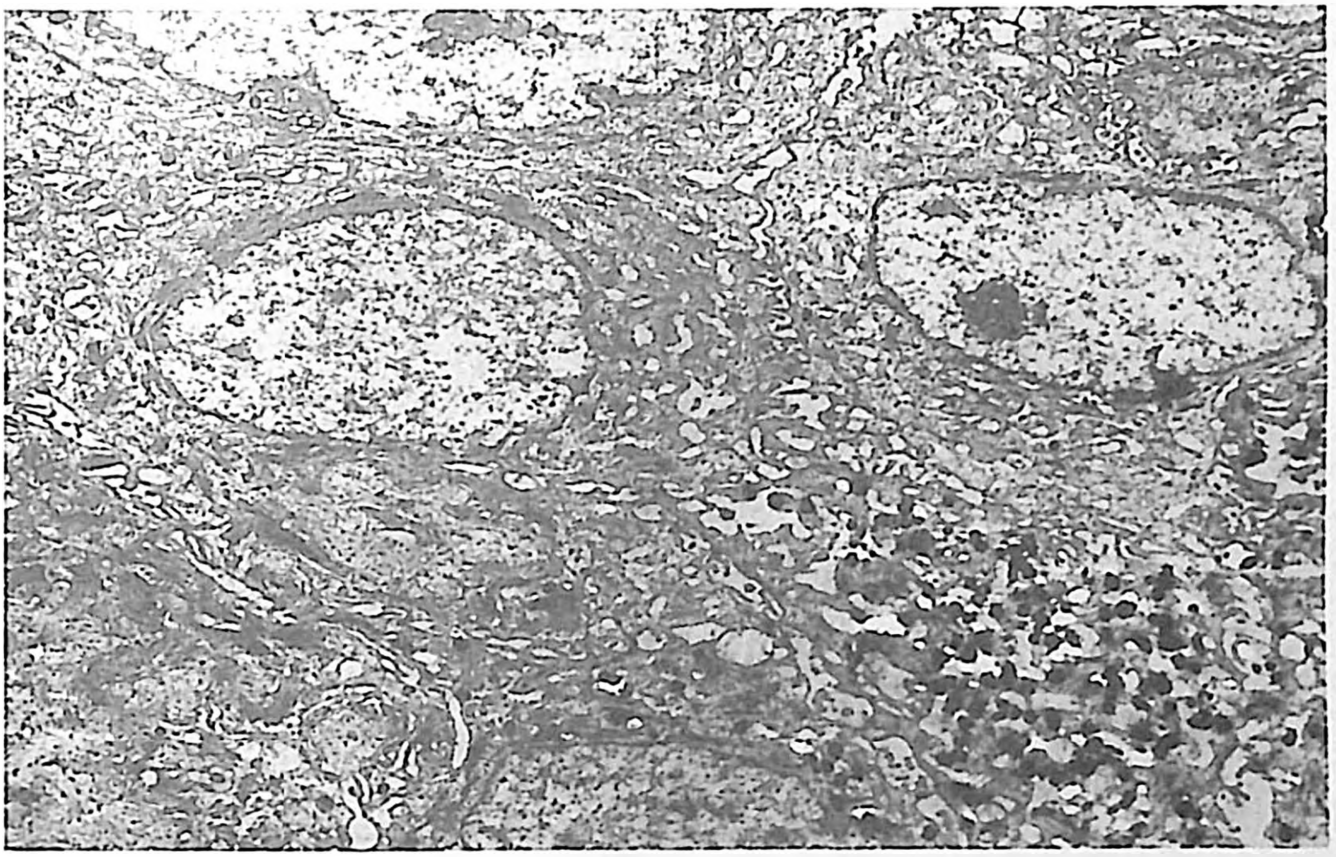

Figure 2.

Electron microscopic appearance of the pigmentation in basal epithelium and loss of normal structure in the desmosomes between the epithelial cells (x3300).

Urinary amino acid excretion was high (3600 mg/24 hours). Serum IgG was 1560 mg/dl, IgM 199 mg/dl and IgA 280 mg/dl. The alpha-1-antitrypsin level was 265 mg/dl.

The serum T_3 (triiodothyronin) value was 100 ng/dl, T_4 (thyroxine) 11 μg/dl and TSH (thyroid stimulating hormone) 7.6 ml U/ml. The metyrapone test was normal. hGH (human growth hormone) response to insulin hypoglycemia was: 0 ng/dl for fasting, 24.2 ng/dl at 60 minutes and 30.0 ng/dl at 120 minutes. Serum somatomedin A activity by bioassay was 0.676 which is within normal limits (normal controls: mean 0.717 ± 0.063 SEM) [5].

Discussion

In 1968 Cleaver demonstrated that fibroblasts from patients with xeroderma pigmentosum showed a defect in repair of UV (ultraviolet)-inflicted DNA damage[6]. The repair rate of fibroblasts in xeroderma pigmentosum patients was only 20% of normal, and this defect was much more pronounced in the DeSanctis-Cacchione variant of the disease[1]. Der Kaloustian et al have studied the enzyme system involved in the repair of UV-damaged DNA and have described 5 subclasses of xeroderma pigmentosum, each caused by a mutation at a different locus, indicating the complexity of the enzyme system involved and also indicating heterogeneity[7]. Clinically distinct entities corresponding to each of the 5 types have not been described. These same authors have predicted that due to this heterogeneity more clinical types of xeroderma pigmentosum would possibly be detected.

The diagnosis of DeSanctis-Cacchione syndrome in our patient was based on the presence of photosensitive freckle-like lesions associated with microcephaly, mental retardation, sensorineural type deafness, choreoathetosis and small stature. Although the initial skin lesions were noted in early life, cutaneous malignancy had not developed until 14 $\frac{8}{12}$ – years of age. Microcephaly was slight when compared with some of the reported cases and neurological damage was limited to mild choreoathetosis and deafness which had developed relatively late. Mental retardation was also of moderate degree. The absence of clinical evidence of disease in other family members suggests a mutant gene of large effect to be the cause of the syndrome in this patient as suggested for other similar cases with no hereditary background[8].

Growth retardation and retardation in sexual development are considered to be among the major symptoms of the syndrome. Autopsy findings in these patients have shown general hypotrophy and small organ weights[1]. Hypogonadism is reported in 50% of the cases[9]. Assessment of bone age appears in only a small number of the case reports and may be normal or retarded for age[1,8]. In our patient, despite the marked growth retardation, sexual development was relatively early. Concomitantly, skeletal maturation was slightly advanced for age. These findings suggest that sexual and skeletal development may remain unaffected by the genetic disorder. Indeed, the age of development of the pubertal signs in this patient, although relatively early, was within the normal variation limits for Turkish girls[4].

The pathogenesis of the marked stunting in growth in DeSanctis-Cacchione patients has, to our knowledge, not been investigated. It is known that hGH deficiency can be associated with a number of syndromes [10,11]. Endocrine studies in our patient have yielded normal T_4 and T_3 levels. hGH secretion as well as somatomedin A activity were within the normal ranges. These findings suggest that the somatic growth defect in DeSanctis-Cacchione syndrome is probably due to a defect in end organ responsiveness at the cellular level associated with the genetic disorder.

The patient is still being observed at regular intervals.

Summary

A 14 $\frac{8}{12}$ - year-old girl with DeSanctis-Cacchione syndrome, characterized by photosensitive freckle-like lesions, microcephaly, mental retardation, sensorineural type deafness, choreoathetosis, and small stature is presented. Endocrine studies revealed normal plasma hGH levels following provocation tests and normal plasma somatomedin levels. A defect in end organ response to somatomedin is suggested as the responsible factor leading to the severe retardation in growth.

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