

## Darier's Disease Associated with Cutis Verticis Gyrata, Hyperprolactinaemia and Depressive Disorder

Emoke Rácz<sup>1</sup>, Zoltán Kornseé<sup>1</sup>, Márta Csikós<sup>1</sup>, Matild Dobos<sup>2</sup>, Pál Salacz<sup>3</sup> and Sarolta Kárpáti<sup>1</sup>

<sup>1</sup>Department of Dermatology, <sup>2</sup>2nd Department of Pediatrics and <sup>3</sup>Department of Psychiatry and Psychotherapy, Semmelweis University Budapest, H-1085 Budapest, Hungary. E-mail: raczem@bor.sote.hu

Accepted May 13, 2005.

Sir,

Cutis verticis gyrata (CVG) is a descriptive term for a thickened scalp condition in which deep furrows, cerebriform or gyriform convoluted ridges are seen (1). It has been classified into primary and secondary types (2). The secondary form has been linked to local inflammatory skin conditions and to systemic illnesses, such as amyloidosis, myxoedema, acanthosis nigricans, acromegaly and pachydermoperiostosis. Chromosomal abnormalities such as Turner syndrome, Klinefelter syndrome, and fragile sites on chromosomes X, 12, and 9 have also been associated with CVG (3–6). Darier's disease (DD) is an autosomal dominantly inherited skin disorder, characterized by loss of adhesion between epidermal cells and abnormal keratinization. The disorder is caused by mutations of the *ATP2A2* gene (12q.23-24.1) encoding a sarco-endoplasmic reticulum calcium ATPase (SERCA2) (7). We describe here a 46-year-old woman with the rare co-occurrence of DD and CVG (8) complicated by endocrinological and psychiatric symptoms.

### CASE REPORT

A 46-year-old woman was diagnosed with DD at the age of 18 years. She has had warty keratin-capped brown papules mostly in the forehead and middle chest (Fig. 1). Longitudinal streaks and distal notches were observed on the nails. Family history was negative for DD. CVG had also been present on the middle forehead and on the occipital region of the scalp since childhood (Fig. 2).



Fig. 1. Darier's disease. Inflamed, confluent dyskeratotic papules on the chest and under the mammae.

Since the age of 22, the patient often had complaints of headache, hypertension, flushing and temporary losses of consciousness. Pregnancy-induced toxemia was also described in the medical history. She observed gradual increase in her body weight. Endocrinological examination revealed acromegaly, hyperprolactinaemia and hypothyreosis behind these symptoms. A microadenoma of the pituitary gland had been discovered. For years, bromocriptin and L-thyroxine therapy was administered and the body weight was reduced by dietary restrictions and regular exercise during repeated hospitalization.

At the time of the genetic studies serum prolactin level was found to be elevated in repeated endocrinological examinations (28 ng/ml; normal range: 3–15 ng/ml). Growth hormone, TSH and FT4 levels were normal. Based on repeated computer tomography scans the pituitary microadenoma is now in complete remission.

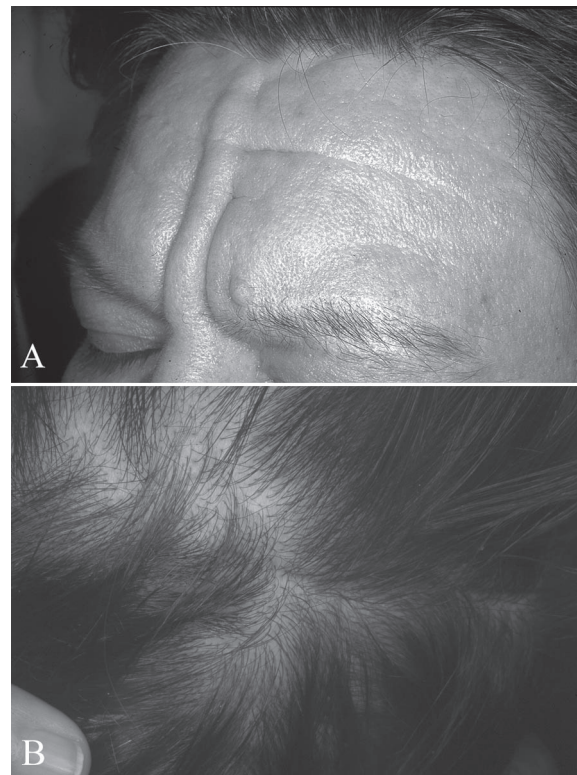


Fig. 2. (A) Cutis verticis gyrata. The hypertrophy and folding of the skin can be seen in the middle of the forehead forming two deep lines in the typical anteroposterior direction. Dyskeratotic papules are also present on the forehead. (B) Deep horizontal folding of the skin in the scalp.

The Beck Depression Inventory (BDI) was administered. The BDI is a 13-item measure of self-reported severity of depressive symptoms with scores between 0 and 39; a score of 6 or higher is the threshold for considering clinical depression. Severity of depression was also assessed using the 21-item version of the Hamilton Rating Scale for Depression (HRSD). The Mini Mental State examination (MMSE) was used to assess general cognitive functioning; general intelligence was measured with the Raven Progressive Matrices. Psychiatric examination of the patient revealed low grade depression diagnosed by HRSD and BDI scales, and normal cognitive and mental functioning.

Studying the *ATP2A2* gene on chromosome 12, in the seventh exon a T-insertion was detected in position 559 (Tins558), which resulted in a premature termination codon (PTC) at codon 192 (9). As CVG has been known to be associated with fragile sites on chromosomes X, 12 and 9, karyotyping of the peripheral lymphocytes had also been performed. Cytogenetic studies were carried out on phytohaemagglutinin-stimulated 72 h lymphocyte cultures. Chromosome analysis was performed by Giemsa-trypsin-Giemsa banding. Karyotyping showed normal female phenotype 46,XX with a 12p terminal chromatid fracture in only one of 74 metaphases, interpreted as a non-significant finding.

## DISCUSSION

Various neurological and psychiatric symptoms have been associated with DD. Likewise, primary CVG is often associated with mental retardation or neuropsychiatric disease. CVG occurs predominantly in men. The onset typically follows puberty, and the folds are usually symmetrical.

Attempting to find a single cause behind the different symptoms of our patient, we performed multiple genetic examinations from peripheral blood leukocytes. Karyotyping had shown 46,XX with a 12p terminal chromatid fracture in only one of 74 metaphases, interpreted as a

non-significant finding. Analysis of the entire coding region of the *ATP2A2* gene (12q.23-24.1) revealed a single nucleotide insertion, Tins558, on one allele of the gene. In this case truncated, non-functional SERCA2 protein may be synthesized, or mRNA may be degraded by the nonsense-mediated RNA decay pathway.

We suppose that CVG in this case was induced by polyendocrinopathy and report the case as an interesting and rare example of the co-occurrence of DD and CVG. The revealed clinical depression could be both secondary to this patient's multiple and difficult to treat diseases and a primary disease often seen with either of her underlying skin disorders.

## REFERENCES

1. Unna PG. Cutis verticis gyrata. *Monatschr Prakt Derm* 1907; 45: 227–233.
2. Polan S, Butterworth T. Cutis verticis gyrata; a review with report of seven new cases. *Am J Ment Defic* 1953; 57: 613–631.
3. Marini R, Cappa M, Neri G, Romana M. Cutis verticis gyrata and chromosomal abnormalities. *Am J Dis Child* 1989; 143: 269–270.
4. Schepis C, Palazzo R, Ragusa RM, Spina E, Barletta C. Association of cutis verticis gyrata with fragile X syndrome and fragility of chromosome 12. *Lancet* 1989; 2: 279.
5. Schepis C, Palazzo R, Cannavo SP, Ragusa RM, Barletta C, Spina E. Prevalence of primary cutis verticis gyrata in a psychiatric population: association with chromosomal fragile sites. *Acta Derm Venereol* 1990; 70: 483–486.
6. Musumeci SA, Ferri R, Viglianesi M, Elia M, Ragusa RM, Bergonzi P. Cutis verticis gyrata and chromosomal fragile sites. *Am J Med Genet* 1991; 38: 249–250.
7. Sakuntabhai A, Ruiz-Perez V, Carter S, Jacobsen N, Burge S, Monk S, et al. Mutations in *ATP2A2*, encoding a Ca<sup>2+</sup> pump, cause Darier disease. *Nat Genet* 1999; 21: 271–277.
8. Parlak M, Erdem T, Karakuzu A, Gulec AI, Akdeniz N. Darier's disease seen with cutis verticis gyrata. *Acta Derm Venereol* 2001; 81: 75.
9. Rácz E, Csikós M, Kornsee Z, Horváth A, Kárpáti S. Identification of mutations in the *ATP2A2* gene in patients with Darier's disease from Hungary. *Exp Dermatol* 2004; 13: 396–399.