Acta Derm Venereol (Stockh) 1990; 70: 483–486

Prevalence of Primary Cutis Verticis Gyrata in a Psychiatric Population: Association with Chromosomal Fragile Sites

CARMELO SCHEPIS[1], ROSARIA PALAZZO[1], SERAFINELLA P. CANNAVO[1], ROSA MARIA RAGUSA[2], COSIMO BARLETTA[3] and EDOARDO SPINA[4]

[1]*Department of Dermatology, University of Messina, Messina and Unit of Dermatology, OASI Institute, Troina (EN),* [2]*Laboratory of Citogenetics, OASI Institute, Troina (EN),* [3] *Department of Haematology, First Institute of Sanity, and* [4]*Psychiatric Hospital, Messina, Italy*

The prevalence of cutis verticis gyrata was studied in a psychiatric institutional population of 494 patients, the majority of whom were mentally retarded or had chronic schizophrenia. Twenty-two subjects (21 males and 1 female) were found to have primary cutis verticis gyrata, yielding a prevalence of about 4.5%. The frequency of the scalp disorder was 11.4% among mentally retarded patients and 1.7% in schizophrenic subjects. A cytogenetic study was performed on patients with primary cutis verticis gyrata. In 9 out of 21 subjects there was evidence of chromosomal fragile sites: 5 patients had fragile sites on the X-chromosome, in 2 there was fragility of chromosome 12 and in 2, fragility of chromosome 9. The fragile X-site is the genetic marker of the 'fragile X-syndrome', a sex-linked inherited disorder often associated with mental retardation and other neuropathological findings. ***Key words: Mental retardation; Schizophrenia; Fragile X-syndrome.***

(Accepted March 12, 1990.)

Acta Derm Venereol (Stockh) 1990; 70: 483–486.

E. Spina, Psychiatric Hospital, U.S.L. 41, Viale Giostra, 98100 Messina, Italy.

Cutis Verticis Gyrata (CVG) is an unusual conformation of the scalp characterized by the presence of folds and furrows due to thickening of the corium and the subcutaneous tissue. In accordance with etiological factors and associated findings, CVG is classified in primary forms of idiopathic nature and secondary forms caused by other disorders of the scalp, such as tumours, nevi, inflammatory conditions, or by systemic diseases, such as acromegaly and pachydermoperiostosis (1).

In primary CVG the folds and the furrows are typically localized between the vertex and the occiput, but can occasionally extend over the entire scalp. The folds are usually symmetrical and disposed in a rather parallel way in the anteroposterior direction. In some instances the folds and the grooves make frequent anastomoses with each other over the scalp, forming a cerebriform appearance.

In secondary forms the involvement of the scalp is usually asymmetrical and the affected portion is distinctly demarcated from the surrounding area. Primary CVG can be divided further into cases that are associated with neuropsychiatric disorders and into essential forms with no known associated disease or antecedent scalp problems (2).

The prevalence of CVG in the Italian population has never been studied systematically, although several cases have been reported (3, 4). In the present study we describe 22 cases of primary CVG that we observed in a psychiatric institutional population. Of particular interest is the finding of the frequent association of this cutaneous malformation with chromosomal abnormalities.

MATERIAL AND METHODS

Over the period January–June 1988 the patients institutionalized at the Psychiatric Hospital, Messina, Italy, were examined to screen out cases of CVG. This population consisted of 494 subjects, 277 males and 217 females, age 24 to 89 years. Of the patients, 299 (159 males and 140 females) were affected by chronic schizophrenia, 149 (92 males and 57 females) were mentally retarded and the other 46 had miscellaneous psychiatric disorders. The Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) was used for psychiatric diagnosis (5). After inspection and palpation, each patient suspected of being affected by CVG underwent total scalp trichotomy to confirm clinical diagnosis. We have classified cases of CVG into mild, moderate, and severe forms with regard to the extension of the involved area and to the number, the depth, the width and the length of folds and furrows.

For histological examination, scalp punch biopsy specimens were taken from patients with CVG and were stained with hematoxylin-eosin, PAS, Weigert-Van Gieson and Mallory. All CVG subjects underwent roentgenography of skull and long bones.

A cytogenetic investigation was carried out in patients

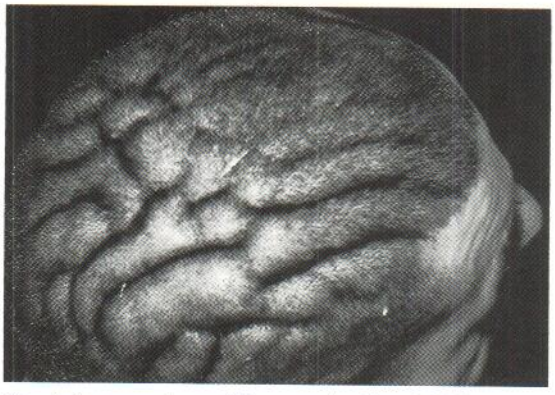

Fig. 1. Severe cutis verticis gyrata (patient D.M.).

with CVG to determine the karyotype and to identify fragile chromosomal sites. Peripheral lymphocytes were isolated from blood samples and cultured *ad modum* Neri et al. (6).

RESULTS

Twenty-two unrelated patients (21 males and 1 female) were found to have primary CVG (Fig. 1). Their ages ranged from 27 to 67 years; 17 were mentally retarded and 5 had chronic schizophrenia. The clinical data from these subjects are summarized in Table I. The cutaneous disorder was asymptomatic in all patients, so that the time of onset of CVG was unknown. Clinical diagnosis was confirmed by histological and radiological investigation. Histological examination revealed no specific abnormality in the epidermis, while in most patients some thickening of collagen bundles and hypertrophy of the pilo-sebaceous apparatus was found in the dermis. Roentgenograms of the skull and long bones were normal with respect to the size of the sella turcica and to the thickness of bones. No case of secondary CVG was identified in our population.

Table I. *Clinical data from patients with primary CVG*

Patient	Sex	Age	CVG	Psychiatric diagnosis	Associated neurologic disorders	Eye defects	% fragile sites[a]
A.L.	M	27	Moderate	Profound MR[b]	Epilepsy	Congenital cataract	–
A.M.	F	38	Moderate	Profound MR	–	–	–
B.D.	M	49	Moderate	Severe MR	–	Strabismus	4% fra (X) (q27)
B.M.	M	50	Moderate	Profound MR	Epilepsy	–	–
C.A.	M	33	Mild	Profound MR	Epilepsy	Nystagmus	–
C.G.	M	61	Mild	Moderate MR	–	–	–
C.N.	M	61	Mild	Schizophrenia	–	–	4% fra (X) (q27)
C.R.	M	64	Moderate	Moderate MR	–	–	–
C.V.	M	60	Mild	Mild MR	–	–	5% fra (X) (q27)
D.M.	M	37	Severe	Profound MR	Epilepsy, paraparesis	–	12% fra (12) (q23)
F.D.	M	37	Moderate	Profound MR	Epilepsy, paraparesis	–	18% fra (12) (q23)
F.F.	M	35	Mild	Profound MR	Epilepsy	Strabismus	–
G.A.	M	33	Moderate	Severe MR	Epilepsy	–	–
G.G.	M	33	Mild	Severe MR	–	–	–
G.L.	M	58	Moderate	Profound MR	–	–	n.d.[c]
L.R.	M	57	Severe	Schizophrenia	–	–	5% fra (X) (q27)
M.C.	M	61	Moderate	Schizophrenia	–	–	10% fra (9) (p21)
M.L.	M	67	Moderate	Schizophrenia	–	–	–
O.A.	M	32	Severe	Profound MR	Epilepsy, paraparesis	–	–
P.V.	M	47	Moderate	Severe MR	–	–	10% fra (9) (p21)
S.G.	M	42	Moderate	Schizophrenia	–	–	–
U.G.	M	62	Moderate	Profound MR	–	–	14% fra (X) (q27)

[a]Number of positive cells on 100 metaphases.
[b]MR = Mental Retardation.
[c]This patient died before cytogenetic analysis.

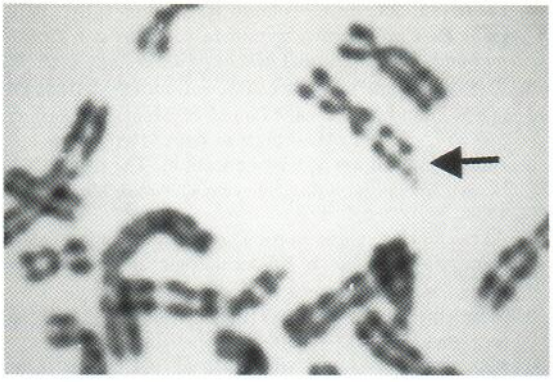

Fig. 2. Fragile X-site (*arrow*) in patient L.R.

Prevalence

The prevalence of primary CVG in our total institutional population was about 4.5%. The corresponding figures in patients with mental retardation and in those with schizophrenia were 11.4% and 1.7%, respectively. If we consider only the male population, the prevalence was 7.6% in the total population, 17.4% in mentally retarded subjects and 3.1% among schizophrenic patients.

Cytogenetic study

All patients with CVG had normal karyotypes: 20 subjects 46,XY and 1 subject 46,XX. One patient died before cytogenetic screening. In 9 patients there was evidence of chromosomal fragile sites: 5 subjects proved to be positive for the marker fra (X) (q27) (Fig. 2), 2 had fragile sites
on chromosome 12 – fra (12) (q23) – and 2 had fragile sites on chromosome 9 – fra (9) (p21). – The proportions of positive cells for each of those subjects are reported in Table I.

DISCUSSION

Primary CVG can be distinguished from secondary forms, particularly cerebriform intradermal nevus and pachydermoperiostosis, on the basis of clinical, histological and radiological examinations. In our investigation of a psychiatric population we have identified only cases of primary CVG that, according to Garden & Robinson (2), can be considered as primary forms associated with a neuropathic disease. Mental retardation and schizophrenia are the psychiatric disorders most commonly associated with CVG. The prevalence of primary CVG in mentally retarded patients has been investigated and found to range from 0.4% to 2.2% (7, 8, 9). The condition is much more frequent in males, in whom the occurrence varies from 0.7% to 3.4%. The association of primary CVG with schizophrenia has been described recently by Chia-Hsiang Chen (10) with a prevalence of about 2% in a male institutional population in China. In the present study we have found a surprisingly high frequency of CVG in mentally retarded patients. In fact the prevalence of CVG in schizophrenic patients, 1.7% (3.1% if we consider only male patients), is about the same as encountered in China. On the other hand, in our study about 11.4% of the total mentally retarded population and 17.4% of the male patients were affected by CVG. Such a high prevalence of CVG in mental retardiation could be related to ethnic factors, since our survey was conducted on a mediterranean island, while previous reports concern North European populations. If this hypothesis were true, it would be difficult, however, to explain the normal prevalence observed in schizophrenia. Moreover the methodology we used might account for the identification of mild forms of CVG, which, without total trichotomy, could have been overlooked.

The other striking result of the present study is the association of primary CVG with chromosomal fragile sites, encountered in 9 out of 21 subjects. Previous cytogenetic studies in patients with CVG reported modifications of the karyotype only sporadically (11, 12). More recently, by using cytogenetic screening for fragile sites, fragility of the X-chromosome and of chromosome 10 was described in 2 mentally retarded patients with CVG (13). As has been mentioned in a preliminary report (14), our group has confirmed this finding. Although the cytogenetic study was carried out only in patients with CVG, the high frequency of association of chromosomal fragility with primary CVG (9/21) cannot be considered casual. With regard to this, Rogers & Simensen (15) have shown that the fragile X-site occurs in about 4–5% of all mentally retarded male subjects while, in a recent survey, no chromosomal defects were found in a sample of 46 male schizophrenic patients (16). Fragile sites on chromosomes 9 and 12 are usually associated with a normal phenotype (17). The fragile site at X (q27) is the cytogenetic marker of the fragile X (fra X) syndrome or Martin-Bell syndrome (18). This is an X-linked inherited disorder, clinically manifest in males, often associated with mental retardation, neuropatholog-

ical findings and minor physical abnormalities (19). In our patients the presence of fragile sites was not related to the severity of the scalp malformation. Some of the typical dysmorphic features of the fra X syndrome (large ears, elongated face, prominent nose, macro-orchidism) where present in 3 out of the 5 subjects in whom the fragile X site was found.

The relatively frequent association of the fra X syndrome with CVG (5/21) suggests that the scalp disorder might represent the cutaneous marker of the syndrome in the adult. Moreover this association could account, at least partly, for the higher frequency of CVG in males. This is in agreement with Akesson (20) who suspected, in 1964, that hereditary sex-linked factors played an important role in the origin of CVG. To explain the disproportion between sexes and the rare onset of CVG before puberty, various authors (7, 9) have suggested the involvement of an endocrine disorder that, up to now, is still unknown. With regard to this an endocrinological screening is presently being carried out in our patients.

In conclusion we believe that CVG is the most common skin disorder in male adult subjects with mental retardation and that some cases of primary CVG might be considered in the future as secondary to the fra X syndrome. Moreover a cytogenetic analysis for the fragile sites should be done in patients with primary CVG associated with neuropsychiatric disorders and/or physical anomalies.

ACKNOWLEDGEMENT

We wish to thank Mr Nino Previti and the nursing staff of the Messina Psychiatric Hospital for their assistence with this study.

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