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Epithalamus calcifications in schizophrenia

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Abstract We evaluated the prevalence and the size of epithalamus calcifications (EC) and choroid plexus calcifications (CPC) on computed tomography (CT) scans in a group of 64 schizophrenic patients and in a group of 31 healthy controls. The associations between cerebral calcifications, demographic variables, and other brain morphological characteristics (particularly cerebral ventricular size and cortical atrophy) in both, patients and controls, were also considered. A significant increase in size of the epithalamic-region calcifications in schizophrenic patients was found, whereas there was no evidence of increase in both, dimension and prevalence, of choroid plexus calcification. Such dimensional increase was unrelated to the duration of illness and therefore did not seem to be iatrogenic or secondary to the disease. A correlation was found between epithalamus calcifications and cortical atrophy and third-ventricle enlargement, suggesting that calcifications of this cerebral region may be associated with lesions of third-periventricular areas and of circuitries hypothesized to be involved in the pathophysiology of schizophrenia.

Key words Schizophrenia · Epithalamus · Habenula · Pineal gland · Computed tomography

Introduction

In the past two decades, structural neuroimaging techniques have demonstrated the presence of various brain morphological abnormalities in schizophrenia (Ratz and Ratz 1990; Lewis 1990; Chua and McKenna 1995), but only few studies have analyzed cerebral calcifications in schizophrenia. In particular, an unexpected high prevalence of pineal calcifications (PC) in schizophrenic patients, especially with early onset, associated with cortical atrophy, EEG abnormalities, drug-induced parkinsonism, and tardive dyskinesia has been observed (Sandyk and Kay 1991 a, b, 1992; Sandyk 1992 a). The frequency of habenular calcifications is also increased in chronic schizophrenic patients (Sandyk 1992 b). A major limitation of these studies was the fact that the authors derived their results from an indirect comparison between their schizophrenic samples and data of a control group reported by Macpherson and Matheson (1979) which was composed of 1000 subjects selected regardless of the presence of organic pathologies (especially neurological conditions) and scanned with a different CT protocol.

The aim of our study was replicate and extend previous findings with better-controlled and larger samples. Since habenular complex is anatomically and functionally linked to the pineal gland (Ronnekleiv and Moller 1979; Ronnekleiv et al. 1980), constituting together the epithalamus (Barr 1979), we evaluated the prevalence and size of epithalamus calcifications (EC) and choroid plexus calcifications (CPC) on computed tomography (CT) scans in a group of schizophrenic patients and in a group of age- and gender-matched healthy controls. Moreover we studied the association between cerebral calcifications, demographic variables, and other brain morphological characteristics in both samples.

Materials and methods

Subjects

The study comprised 64 patients with schizophrenia diagnosed according to DSM-III-R criteria (American Psychiatric Association 1987; Table 1). There were 40 males and 24 females, with a mean age of 25.9 years (SD 6.8 years, age range 16–45 years), a mean age of onset of 20 years (SD 4.5 years); mean duration of illness 5.7 years (SD 5.4 years). The control group consisted of 31 subjects, 16 males and 15 females, with a mean age of 26.8 years (SD 9.4 years, age range 13–57 years) who had undergone cerebral CT scan as a routine diagnostic examination for minor head trauma without loss of consciousness. The general criteria for inclusion were: (a) absence of medical or neurological illness possibly responsible for neuromorphological alterations; (b) no corticosteroid

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Table 1 Demographic characteristics of the study sample

Subjects	64 patients (diagnosis of schizophrenia; DSM-III-R criteria)	31 controls (minor accidental head trauma without sequelae)
Gender	40 males, 24 females	16 males, 15 females
Age (years)	25.9 ± 6.8 (range 16–45)	26.8 ± 9.4 (range 13–57)
Age of onset (years)	20 ± 4.5	
Duration of illness (years)	5.7 ± 5.4	

intake in the 3 months preceding the study; (c) no history of alcohol or drug abuse or head trauma with loss of consciousness; and (d) no previous electroconvulsant therapy. All controls were assessed clinically to exclude any psychiatric disturbances or a family history of schizophrenia in first-degree relatives.

The age of onset was considered as the age at which psychotic symptoms first appeared as reported by the patients themselves and their parents. Among the patients, family history (FH) for schizophrenia, collected from the patient himself and from at least one healthy relative, was assessed in 58 cases (FH+, $n = 10$; FH–, $n = 48$).

Family history was only examined for the first-degree relatives (parents, brothers/sisters, children), and we only considered a positive FH for schizophrenia (FH+; for more details see Vita et al. 1994a).

All subjects included in this study were previously considered in other papers of our group (see Vita et al. 1994a), but no data on EC and CPC have been published by us previously.

CT measurements

Patients and controls were examined by means of a GE 9000 II CT Scanner (General Electric, Milwaukee, Wis.). Ten-millimeter-thick slices, parallel to the canthomeatal line, were obtained from all subjects. Epithalamus calcifications as well as right and left CPC were identified on scans and categorized from the largest to the smallest by two expert raters (M.D. and G.M.G.) blind to the diagnosis. Scans were classified when both raters reached agreement on the relative dimension of the calcification and received a progressive number of order for each structure evaluated, except two EC scans, two right CPC scans, and two left CPC scans that were consequently excluded from the analysis. Nineteen scans without EC were assigned a zero value. Epithalamus calcifications were present (see Fig. 1) in the remaining 74 scans that were numbered from 1 to 74 according to their dimension. Differently from Sandyk and Kay (1991a), who used a dimensional criterion (diameter ≥ 1 cm), we considered enlarged the 33% of 93 scans (from numbers 43 to 74) having the larger calcification (see Fig. 2). The same method was used for classifying right and left CPC.

Epithalamus calcifications included pineal gland and habenular calcification. Although some authors (Sandyk 1992b) divided the two structures, we could not clearly distinguish pineal and habenular calcifications in 36 of 95 scans (37.8%). This was due to the fact that in some cases the calcification was present in the recessus (recessus suprapinealis or pinealis) of the gland, a structure barely discernible from the body of the gland and the adiacent habenular commissure. Therefore, we preferred to use a more reliable evaluation instead of a more site-specific one.

Lateral ventricular size was measured with a semiquantitative method on digitalized scan images (RAS 2000 System, Amersham Int., Berkhamsted, Hertfordshire, UK), on the CT section in which the lateral ventricles appeared largest. Lateral ventricular size was expressed as the ratio of the ventricular area to the total brain area × 100 (VBR) (Synek and Reuben 1976).

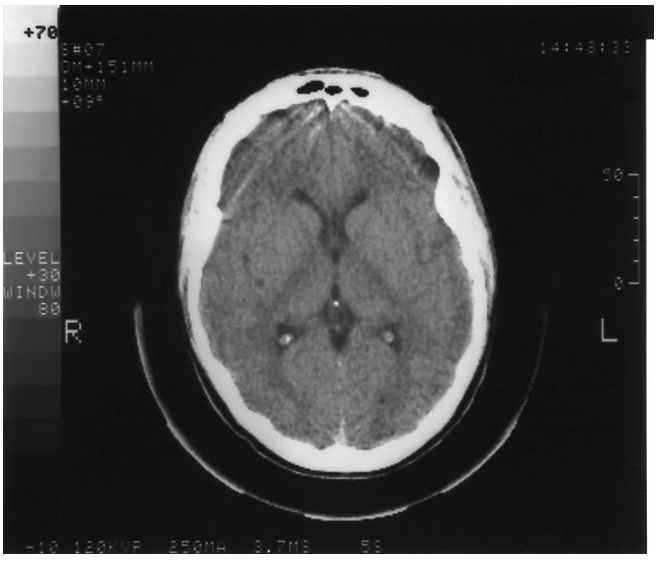

Fig. 1 Example of a present epithalamus calcification

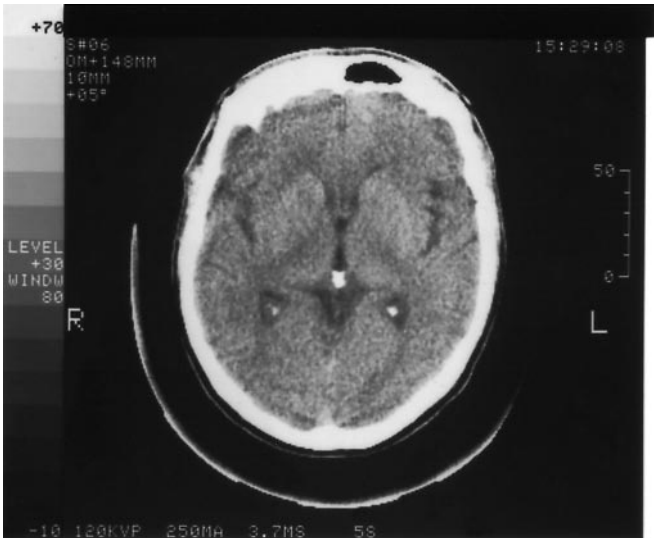

Fig. 2 Example of an enlarged epithalamus calcification

Cortical atrophy, a neuroradiological definition of cortical sulci appearance, was measured with a 4-point visual scale, assessing increasing degrees of widening of the cortical sulci and the interhemispheric and sylvian fissures (0 = absent; 1 = uncertain/mild; 2 = moderate; 3 = severe; Vita et al. 1988). The rating was made by using a reference image for each atrophy class of the same scanner.

Third-ventricle width (TVW) was expressed as a ratio of the largest width of the third ventricle with the anteroposterior (AP) diameter, defined as the line connecting the frontal and occipital poles on a midline passing through the third ventricle (Kanba et al. 1987). Our raters assessed the scans independently, blind to the diagnosis, and the inter-rater reliability of these last three measurements was calculated on scans of a 20-subject random sample (VBR: Pearson's $r = 0.94$; Cortical atrophy: Cohen's $K = 0.82$; TVW: Pearson's $r = 0.88$).

Statistical analyses

Analysis of variance for ordered values was used as suggested by Conover and Iman (1981). Chi-square test was used when fre-

quencies were compared. Spearman rank coefficient was used for correlation analyses of the non-parametric data.

Results

Calcifications, diagnosis, and gender

In a model considering EC-ordered values as a dependent variable and diagnosis and gender as independent variables, we found a significant effect of diagnosis ($F = 6.02$; $df = 1, 89$; $p = 0.016$), with patients showing EC-ordered values, and hence EC dimensions, higher than that of controls (33.5 ± 24.1 vs 20.4 ± 22.2). No effect of gender emerged (mean EC for males: 31 ± 24; mean EC for females: 26.3 ± 24.4; $F = 0.48$; $df = 1, 89$; p = n.s.) nor any effect of the diagnosis by gender interaction ($F = 2.64$; $df = 1, 89$; p = n.s.). Moreover, there was no significant effect on right and left CPC number of order of diagnosis, gender, or their interaction. The patients' EC prevalence (52 of 62, 84%) did not significantly differ from that of controls (22 of 31, 71%; $\chi^2 = 2.12$, p = n.s.), whereas the frequency of enlarged EC in patients (26 of 62, 42%) was significantly higher than that in controls (5 of 31, 16%; $\chi^2 = 6.2$, $p = 0.01$). No difference emerged for right CPC prevalence (patients: 44 of 62, 71%; controls: 21 of 31, 68%; $\chi^2 = 0.10$, p = n.s.), left CPC prevalence (patients: 47 of 62, 76%; controls: 21 of 31, 68%; $\chi^2 = 0.68$, p = n.s.), rate of enlarged right CPC (patients: 20 of 62, 32.3%; controls: 12 of 31, 38.7%; $\chi^2 = 0.14$; p = n.s.) and of enlarged left CPC (patients: 23 of 62, 37.1%; controls: 10 of 31, 32.3%; $\chi^2 = 0.05$, p = n.s.).

Regarding calcifications, age, age of onset, and duration of illness, the correlations are shown in Tables 2 and 3.

Regarding calcifications, VBR, TVW, and cortical atrophy, the correlations are shown in Tables 4 and 5.

Table 2 Correlations of calcifications, age, age of onset, and duration of illness in schizophrenic patients. *EC* epithalamus calcifications; *CPC* choroid plexus calcifications

	Age	Age of onset	Duration of illness
EC	ρ = 0.17	ρ = 0.17	ρ = 0.06
Right CPC	ρ = 0.06	ρ = 0.04	ρ = –0.11
Left CPC	ρ = 0.19	ρ = –0.01	ρ = 0.01

All correlations non-significant at 0.05

Table 3 Correlations of calcificiations and age in control subjects. All correlations non-significant at 0.05

	Age
EC	ρ = –0.09
Right CPC	ρ = 0.34
Left CPC	ρ = 0.027

Table 4 Correlations of ratio of ventricular area to total brain area × 100 (*VBR*), third-ventricle width (*TVW*), cortical atrophy, and calcifications in schizophrenic patients

	EC	Right CPC	Left CPC
VBR	ρ = 0.06	ρ = 0.32**	ρ = 0.23
TVW	ρ = 0.29**	ρ = 0.10	ρ = –0.05
Cortical atrophy	ρ = 0.27*	ρ = –0.04	ρ = –0.03

* $p < 0.05$; ** $p < 0.03$

Table 5 VBR, TVW, cortical atrophy, and calcifications in control subjects

	EC	Right CPC	Left CPC
VBR	ρ = 0.09	ρ = 0.01	ρ = –0.13
TVW	ρ = 0.16	ρ = 0.25	ρ = 0.20
Cortical atrophy	ρ = 0.23	ρ = –0.39**	ρ = 0.22

** $p < 0.03$

Calcification and family history

Among patients, EC-ordered values did not differ between FH+ and FH- subjects (FH+: $n = 10$, mean 32.6 ± 29.2; FH-: $n = 48$, mean 34.3 ± 22.1; $F = 0.046$; $df = 1, 58$; p = n.s.). However, EC prevalence was significantly higher among FH- patients (43 of 46, 93%) than among FH+ patients (6 of 10, 60%; $\chi^2 = 5.63$, $p = 0.018$ with Yates correction). Frequency enlarged EC was similar in both FH- (19 of 46, 41%) and FH+ (5 of 10, 50%) patients; $\chi^2 = 0.3$, p = n.s.). Right and left CPC size was not affected by FH.

Discussion

Although EC prevalence was not different between patients and controls, schizophrenic subjects showed EC size greater than controls as demonstrated by both the comparison of the ordered numbers and of the frequency of enlarged calcifications in the two groups. These findings are partially comparable with those of Sandyk and Kay (1991 a), who reported an unexpected rate of pineal calcifications, and with Sandyk (1992 b), who reported habenular calcifications, in schizophrenic patients. In our sample, we were able to demonstrate a size difference between patients and controls, but not a significant difference in the rate of subjects with calcifications.

Our study confirms the data by Sandyk and Kay (1991 a) of a greater prevalence of pineal calcification with a diameter ≥ 1 cm in schizophrenic patients (11.8 vs 1% expected) with respect to the increased frequency of the gland calcification (78.4 vs 30–50% expected).

The lack of correlation between calcification size and duration of illness makes unlikely that epithalamic hypercalcification could be a neurodegenerative or an iatrogenic process. This point suggests that such an abnormality, like other neuromorphological alterations (Vita et al. 1994 b; Vita et al. 1997), represents an early event of the disease.

Moreover, EC size differences could not be attributed to an age effect, since age was not correlated to EC in patients and controls. Although an age-related increase in pineal calcification has been demonstrated in normal subjects (Trentini et al. 1987), the lack of such a finding could be due to the low sample size and to the narrow age range among the controls selected for this study.

In healthy subjects EC is a physiological process that partly reflects pivotal changes in the secretory activity of the pineal gland (Trentini et al. 1987). Although this process occurs with a wide range of features, the rate of EC increases with advancing age (Sutton 1975; Sack et al. 1986), significantly during puberty (Trentini et al. 1987; Macpherson and Matheson 1977; Zimmermann and Bilaniuk 1982), during the third decade (Mcpherson and Matheson 1979) and in the postmenopausal period (Trentini et al. 1987). The mechanism of calcification and its significance are not yet clear. Cooper (1932) stated that the calcareous body histologically seen originated from the parenchymal-cells cytoplasm. The disintegration of the cells and the subsequent liberation of the calcareous material was assumed to be due to retrogressive changes. These changes, in normal subjects, may be influenced by race, gender, age, metabolic status, endocrine disease, light exposure, and drug intake (Welsh 1985; Trentini et al. 1987).

The meaning of abnormal EC in schizophrenic patients remains to be clarified. Sandyk (1991a, b) proposed that abnormal pineal calcification could reflect the past secretory activity of the gland and that a reduction of melatonin secretion may be involved, through a lack of mesolimbic and mesocortical dopaminergic activity inhibition. Although this is an intriguing hypothesis, a decrease in serum melatonin levels has been demonstrated only after the onset of the disease (Sandyk 1991a), and the antidopaminergic activity of melatonin has been proved only in animal models.

An alternative explanation may result from the neurodevelopmental hypothesis of schizophrenia (Weinberger 1987). This model implicates a "lesion" of subcortical–cortical circuitry: a functional alteration of this circuitry has been demonstrated in schizophrenia with single photon emission computed tomography (SPECT; Rubin et al. 1994). Epithalamus, and in particular habenula, through fasciculus retroflexus receives a massive output to raphe nuclei, substantia nigra, ventral tegmental area (VTA), as well as reticular and central gray structures (Nauta 1958; Nievwenhuys 1988; Ellison 1994). Epithalamus is a crucial connecting point for the dorsal diencephalic conduction system, a crossroad for caudally directed pathways, and one of the few interpasses where striatal and limbic projections directly intermix (Nauta 1958). Through stria medullaris, the lateral habenula receives descending pathways from frontal cortex as well as striatal and limbic dopamine-rich structures which exert a large inhibitory influence over mesencephalic and diencephalic centers controlling reward, punishment, nociception, and other complex primitive behaviors (Nauta 1958; Nievwenhuys et al. 1988; Ellison 1994).

Moreover, the correlation between EC size, third-ventricle width, and cortical atrophy confirmed Sandyk's findings (1991a, b) and can be interpreted as the effect of a primary subcortical damage involving the cortico-subcortical feed-back circuits, causing third-ventricle enlargement and abnormal EC. Cortical damage may subsequently develop, resulting in cortical atrophy.

Regarding CPC, no differences in prevalence and size were found between patients and controls. This indicates that EC size increase is not due to some general metabolic event. Moreover, there was no correlation between CPC size and duration of illness, but right and left CPC size were correlated with age in the control group. In the case of EC, we found a different pattern of association between calcification process and age: CPC size tended to increase with age in healthy subjects (Macpherson and Matheson 1979) but not in schizophrenics. Moreover, CPC size correlated with cortical atrophy and third-ventricle width in controls: this was not an unexpected result since a progressive process of cortical atrophy and CPC is physiologically age related (Macpherson and Matheson 1979).

Another interesting finding was the association between EC and family history for schizophrenia. The FH+ patients showed a significantly lower absolute EC rate, with an enlarged EC rate being higher in FH- patients. This point adds further evidence to the hypothesis of partially different biological correlates in "familial" and "sporadic" forms of schizophrenia (Vita et al. 1994a).

Conclusion

Our data show a significant increase in the degree, but not in the frequency, of epithalamic region calcifications in schizophrenia. On the other hand, there is no evidence of increase in both dimension and prevalence of choroid plexus calcifications. Such dimensional increase is unrelated to the duration of illness, does not seem to be iatrogenic or secondary to the disease, and points to a neurodevelopmental origin of schizophrenia.

The anatomo-functional connections of epithalamus with limbic dopamine-rich structures and with descending pathways from frontal cortex (Ellison 1994), and the correlation with cortical atrophy and third-ventricle enlargement, indicate that EC may be associated with a lesion of third periventricular areas close to the limbic system and of those cortico-subcortical pathways hypothesized to be involved in the pathophysiology of schizophrenia.

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