Reduced cortical folding of the anterior cingulate cortex in obsessive–compulsive disorder

Geumsook Shim, MD; Wi Hoon Jung, MS; Jung-Seok Choi, MD; Myung Hun Jung, MD; Joon Hwan Jang, MD; Ji-Young Park, MS; Chi-Hoon Choi, MD, PhD; Do-Hyung Kang, MD, PhD; Jun Soo Kwon, MD, PhD

Shim, J.S. Choi, M.H. Jung, Jang, Kang, Kwon — Department of Psychiatry, Seoul National University College of Medicine; W.H. Jung, Park, Kwon — Neuroscience Institute, SNU-MRC; C.H. Choi — Department of Radiology, National Medical Center, Seoul, Korea

Background: Anterior cingulate cortex (ACC) abnormalities have been implicated consistently in the pathophysiology of obsessive–compulsive disorder (OCD), yet it remains unclear whether these abnormalities originated during early neurodevelopment. In this study, we examined the ACC sulcal/gyral patterns to investigate whether neurodevelopmental anomalies of the ACC were present in patients with OCD. We hypothesized that patients with OCD would show reduced cortical folding of the ACC compared with controls.

Methods: We used magnetic resonance imaging (MRI) of 169 healthy volunteers and 110 patients with OCD to examine the paracingulate sulcus and cingulate sulcus. We assessed cortical folding patterns according to established classification criteria and constructed 3 categories of paracingulate sulcus morphology according to its presence and anteroposterior extent: “prominent,” “present” and “absent.” We classified the cingulate sulcus as “interrupted” or “continuous” according to the interruptions in its course. In addition, we evaluated ACC sulcal asymmetry based on interhemispheric comparisons of paracingulate sulcus morphology. Results: Analyses revealed that patients with OCD were significantly less likely than controls to show a well-developed left paracingulate sulcus: 50.0% of patients and 65.1% of controls showed a “prominent” or “present” paracingulate sulcus in the left hemisphere. However, there were no differences in regard to cingulate sulcus continuity, and patients also showed the same leftward ACC sulcal asymmetry as controls.

Limitations: Our study was limited by the fact that we obtained the MRI scans from 2 different scanners, and we did not calculate cerebral fissurization as our study was restricted to 1 specific brain region. Moreover, patients and controls differed significantly in terms of sex ratio and IQ, although we controlled these variables as covariates. Conclusion: Our findings imply a subtle deviation in the early neurodevelopment of the ACC in patients with OCD, but the extent to which these anomalies contributed to the pathogenesis of OCD remains unclear. Further studies that link the ACC morphologic anomalies to the pathophysiology of OCD are recommended.

Introduction

Abnormal structure and function of the anterior cingulate cortex (ACC) has been commonly reported among individuals with obsessive–compulsive disorder (OCD), namely decreased grey matter, lower N-acetylaspartate levels, reduced glutamate/glutamine concentrations and hyperactivity in the resting and symptom-provoked state. The ACC represents a specialized area of the neocortex devoted to the regulation of emotional and cognitive behaviour and plays a major role in executive processes. Numerous studies have shown that patients with OCD exhibit some cognitive deficits, including executive and visual memory dysfunctions, and that these impairments might be related to the ACC dysfunction.

The paracingulate cortex occupies a large portion of the dorsal part (termed the “cognitive” division) of the ACC. The ACC shows substantial variations in sulcal/gyral patterns, including those involving the paracingulate sulcus and cingulate sulcus. Cortical folding is formed primarily during the second and third trimesters of gestation and remains relatively stable after birth; cerebral sulcal/gyral patterns (and their asymmetries), rather than their volumes, are supposed to be robust in their resistance to illness and...
treatment.\textsuperscript{19,20} That is, such patterns provide useful information about the contributions of neurodevelopmental factors to the etiology of illnesses.

Obsessive–compulsive disorder could be considered a neurodevelopmental disorder based on the commonalities between it and schizophrenia (i.e., the same neural substrates, including the frontostriatal circuit and serotonin/dopamine systems, and the higher co-occurrence rates than expected).\textsuperscript{21,22} Frequent onset in childhood (about 80%),\textsuperscript{23} substantially impaired neurologic functions\textsuperscript{24,25} and comorbidity with Tourette syndrome\textsuperscript{25} also support the neurodevelopmental model of OCD. Anatomic brain asymmetries are apparent by the second trimester of gestation and are associated with neurodevelopmental processes;\textsuperscript{26,27} the neurodevelopmental model of schizophrenia underscores data showing that the latter is characterized by anomalies of lateralization.\textsuperscript{28} Recently, by examining paracingulate and cingulate sulcal patterns, Yücel and colleagues\textsuperscript{29} reported that patients with schizophrenia were less likely to manifest a well-developed “prominent” paracingulate sulcus in the left hemisphere, resulting in a lack of the “normal” leftward asymmetry. In addition, individuals at ultra-high risk for psychosis also showed similar ACC anomalies.\textsuperscript{30}

As mentioned, although the ACC has been consistently implicated in the pathophysiology of OCD, evidence to determine the neurodevelopmental origins of this condition remains scarce. To investigate whether neurodevelopmental anomalies of the ACC were present in patients with OCD, we examined the paracingulate and cingulate sulcus morphology according to the established classification criteria. We hypothesized that patients with OCD would show reduced cortical folding of the ACC compared with controls.

Methods

Participants

We recruited patients with OCD from the OCD clinic at Seoul National University Hospital between July 1998 and March 2008. These patients fulfilled the DSM-IV\textsuperscript{31} criteria for OCD, as diagnosed using the Structured Clinical Interview for DSM-IV.\textsuperscript{32} In addition, we recruited healthy controls from the community through newspaper or Internet advertisements. In controls, we confirmed the absence of psychiatric disorders using the Structured Clinical Interview for DSM-IV, nonpatient edition.\textsuperscript{33} We assessed handedness using Annett’s questionnaire.\textsuperscript{34,35} Exclusion criteria for all groups were as follows: a history of clinically important head injury, seizures, neurologic diseases, a clinically important medical illness, IQ less than 70 and DSM-IV criteria of alcohol or substance abuse or dependence.\textsuperscript{36} We excluded controls with a personal or family history of psychiatric illness.

Although OCD was the primary clinical diagnosis of patients, we noted whether they had additional axis I or II DSM-IV diagnoses. We also noted whether patients were taking medications at the time of scanning. We measured the severity of symptoms with the Yale–Brown Obsessive–Compulsive Scale.\textsuperscript{37,38}

The Institutional Review Board at Seoul National University Hospital approved our study, and participants provided written informed consent, including parental consent for those younger than 18 years.

MRI protocol

Scanning took place at 2 different sites: Seoul National University Hospital and the National Medical Center. We acquired T\textsubscript{1}-weighted spoiled gradient echo MRIs on a 1.5 T Signa system (General Electric) at Seoul National University Hospital. We loaded all MRIs obtained at this location into the Analyze image-processing software package and spatially realigned them along the anteroposterior axis of the brain parallel to the intercommissural line. At the National Medical Center, we obtained T\textsubscript{1}-weighted high-resolution structural images on a 1.5 T Magnetom Avanto scanner (Siemens) using a magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence. Since the anterior–posterior commissural line was aligned horizontally at the time of image acquisition at the National Medical Center, image processing was not required. Imaging parameters at Seoul National University Hospital were as follows: 1.5 mm sagittal slices, echo time (TE) 5.5 ms, repetition time (TR) 14.4 ms, flip angle 20°, matrix size 256 × 256, field of view (FOV) 21 × 21 cm and voxel dimensions 0.82 × 0.82 × 0.82 mm. Imaging parameters at the National Medical Center were as follows: 0.9 mm axial slices, TE 4.76 ms, TR 1160 ms, flip angle 15°, matrix size 256 × 256, FOV 23 × 23 cm and voxel dimensions 0.45 × 0.45 × 0.90 mm. Each scanner was calibrated every month with the same phantom to ensure stability of measurements across time. We used code numbers to ensure patient confidentiality and blind ratings. We performed image analysis using MRIcon (Version β, 31 March 2008) and Analyze (Version 8.1, Biomedical Imaging Resource, Mayo Clinic).

Classification of anterior cingulate morphology

Paracingulate and cingulate sulcus classification criteria

We used the protocol developed by Yücel and colleagues\textsuperscript{39} to classify the paracingulate sulcus in each hemisphere. This method, established as reliable, yielded 3 categories of paracingulate sulcus morphology: “prominent,” “present” and “absent” (Fig. 1). We defined the paracingulate sulcus as the sulcus running dorsal and parallel to the cingulate sulcus. Briefly, we considered the paracingulate sulcus to be “prominent” if there was at least 1 clearly developed sulcus with either a length equal to or greater than 40 mm or interruptions totalling 20 mm or less. When the interruptions were greater than 20 mm, we classified the paracingulate sulcus as either “present” if it was at least 20 mm long or “absent” if it was less than 20 mm long. We classified the cingulate sulcus as “interrupted” if there were 1 or more clear interruptions in its course, present for at least 3 adjacent slices; we classified it as “continuous” if such interruptions were not evident (Fig. 1). This cingulate sulcus classification was based on methods described by Paus and colleagues,\textsuperscript{15} but we measured only the
interruptions between the anterior origin of the cingulate sulcus and the imaginary vertical line passing through the anterior commissure, and we did not consider length (i.e., the interrupted gap) in our study to focus on the ACC morphology and increase sensitivity (“interrupted” criteria in Paus and colleagues’ article required a gap ≥ 10 mm).

One of us (G.S.) completed all classifications. To classify ACC morphology, the rater obtained the midsagittal section and moved 7–8 slices laterally from the midline. As indicated in a previous study,14 assessing ACC morphology over several parasagittal slices is important to discriminate the paracingulate or cingulate sulcus from superficial dimples and to avoid MRI sampling error effects. We established both intra- and inter-rater reliabilities for the classification of ACC morphology using 48 randomly chosen cases (96 hemispheres). Intra- (G.S.) and inter-rater (G.S. and W.H.J.) reliabilities (weighted κ statistic) for the classification of the paracingulate sulcus were κ = 0.79 and κ = 0.80, respectively; intra- and inter-rater reliabilities for the classification of the cingulate sulcus continuity were κ = 0.86 and κ = 0.87, respectively. Both raters were blind to participant details at all times.

**Anterior cingulate asymmetry index**

We derived an asymmetry index from differences between left and right hemisphere paracingulate sulcus morphology as previously described.14 In brief, we considered “prominent,” “present” and “absent” values to reflect the magnitudes of paracingulate sulcus explicitness. Accordingly, an asymmetry index could be assigned to each individual; this index consisted of 5 categories (left >> right, left > right, left = right, left < right, left << right) derived from the 9 combinations of left versus right paracingulate sulcus classifications. Leftward (left >> right, left > right) and rightward (left < right, left << right) asymmetries could be graded as a one-category difference (“>” or “<”); “present” v. “absent” or “present” v. “prominent,” respectively) or a 2-category difference (“>>” or “<<”: “prominent” v. “absent” or “absent” v. “prominent,” respectively). The asymmetry index indicates whether the folded paracingulate sulcus was symmetric or asymmetric as well as the direction and magnitude of such folding.20

**Statistical analyses**

We performed all analyses using SPSS 12.0K for Windows (SPSS Inc.), and we set statistical significance at p < 0.05. First, we examined the effect of diagnostic group on paracingulate sulcus morphology using the likelihood ratio test for trend, in which the morphology of the left or right hemisphere (with 3 ordered categories) or the asymmetry index (with 5 ordered categories, as described previously) represented the dependent variable. In addition, we examined the effect of diagnostic group on cingulate sulcus continuity (with 2 ordered categories) using the likelihood ratio χ² test. We used McNemar’s test for symmetry35 to test whether the number of cases of ACC asymmetry in one direction was counterbalanced by an equal number of cases with an asymmetry in the other direction. A significant value indicated an asymmetric pattern, that is, a greater explicitness of cortical folding in one direction.

To examine interaction effects on ACC morphology, we further examined the effect of diagnostic group on ACC morphology using binary or polychotomous logistic regression36 in which the cingulate or paracingulate sulcus classification or the asymmetry index represented the dependent variable for each analysis. In these analyses, we used diagnostic group, sex and IQ as independent variables and covariates.

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Fig. 1: Magnetic resonance images of 3 left hemispheres (upper panels) and their corresponding line drawings (lower panels) illustrate the variations in paracingulate and cingulate sulcus morphology. The vertical dashed line represents an imagery vertical line passing through the anterior commissure, the white solid line represents the paracingulate sulcus and the black solid line represents the cingulate sulcus.
Results

Participants

Of the 289 individuals meeting the inclusion criteria before scanning, we included 279 in the study (110 patients with OCD and 169 controls). We excluded 10 after MRI scanning: 4 patients with OCD (1 owing to poor image quality, 1 owing to mental retardation, and 2 owing to substance abuse history) and 6 controls (1 owing to poor image quality, 3 owing to mental retardation, and 2 owing to family history of psychiatric illness). Twenty-six patients had additional axis I or II DSM-IV diagnoses as follows: depressive disorder (n = 15), tic disorder (n = 6), depressive disorder with social phobia (n = 1), depressive disorder with tic disorder (n = 1), depressive disorder with obsessive–compulsive personality disorder (n = 1), tic disorder with attention-deficit hyperactivity disorder (n = 1) and obsessive–compulsive personality disorder (n = 1). Twenty-eight patients were taking medications at the time of scanning; 11 were taking selective serotonin reuptake inhibitors (SSRIs) with atypical antipsychotics and 16 were taking SSRIs without atypical antipsychotics. The medication profile was not available for 1 patient. Thirty-three patients were drug-naïve and 43 were medication-free for at least 4 weeks before scanning. Treatment data were not available for 6 patients. Scanning occurred at Seoul National University Hospital for 68 patients and 68 controls and at the National Medical Center for 42 patients and 101 controls. Participant demographic and clinical characteristics are presented in Table 1. Patients and controls differed significantly in terms of sex distribution, education level and IQ.

Paracingulate and cingulate sulcus morphology

Consistent with other studies, we found that ACC morphology was extremely variable within and between hemispheres. Across hemispheres, 53.0% of controls and 42.3% of patients showed evidence of a paracingulate sulcus in either its “present” or “prominent” form, whereas 84.6% of controls and 81.8% of patients showed evidence of a “continuous” cingulate sulcus.

The presence of a paracingulate sulcus (“prominent” or “present”) was more frequent in the left hemisphere than in the right hemisphere for both groups (controls: χ² = 20.17, p < 0.001; patients: χ² = 5.41, p = 0.020). Patients with OCD were significantly less likely than controls to have a “prominent” or “present” paracingulate sulcus (by about 15%) and more likely to have an “absent” paracingulate sulcus in the left hemisphere (χ² = 6.38, p = 0.041; Fig. 2). This result was maintained after partialling out the effects of sex and IQ (χ² = 6.65, p = 0.036). There were no significant differences between controls and patients in regard to paracingulate sulcus morphology in the right hemisphere (unpartialled: χ² = 2.77, p = 0.25; partialled: χ² = 1.89, p = 0.39). As we used different scanners, we also compared the frequencies of the paracingulate sulcus classifications between 2 scanners and found no significant differences between the 2 scan sites in the paracingulate sulcus classifications of patients (left: χ² = 0.006, p = 0.99; right: χ² = 4.62, p = 0.10) or controls (left: χ² = 2.98, p = 0.23; right: χ² = 1.57, p = 0.46).

Table 2 shows the proportions of participants with a continuous or interrupted cingulate sulcus. The 2 groups did not differ significantly in terms of continuity in both hemispheres, and there were no significant main effects of sex or IQ on cingulate sulcus continuity.

Anterior cingulate asymmetry

The McNemar test for symmetry showed a significant asymmetry for both groups, indicating a biased distribution of...
effects of sex or IQ on the asymmetry index measure. We further examined asymmetry of the paracingulate sulcus using the asymmetry index measure, which enabled the use of polychotomous logistic regression statistics (see Methods section), as shown in Table 3. A direct comparison of the 2 groups in terms of the asymmetry index measure showed no significant difference, and there were no significant main effects of sex or IQ on the asymmetry index measure.

Discussion

To our knowledge, ours represents the first study to examine the surface morphology of the ACC in a large sample of patients with OCD. Patients with OCD were less likely than controls to have a well-developed paracingulate sulcus in the left hemisphere, but there was no difference in cingulate sulcus continuity between the 2 groups. The pattern of paracingulate folding showed a leftward bias in both groups. These findings were not attributable to the differences in the sex ratio and IQ results between the 2 groups since there was no relation between sex or IQ and ACC morphological patterns.

Flor-Henry has proposed that left frontal lobe dysfunction characterizes OCD, and numerous studies, including those involving electrophysiology, neuropsychological tests and structural/functional neuroimaging, have supported this view. Within this perspective, the reduced cortical folding observed in the left ACC in our OCD sample can be considered to represent left-sided disturbances in brain morphology in patients with OCD. However, several other studies have supported right hemisphere dysfunction in OCD, thus indicating that evidence for lateralized hemisphere pathology in OCD remains inconclusive.

![Graph showing proportion of paracingulate sulcus morphologic classifications](image)

**Fig. 2**: Proportion of paracingulate sulcus morphologic classifications. The likelihood ratio test for trend showed a significant difference between patients with obsessive–compulsive disorder and controls for the left paracingulate sulcus classifications; patients were significantly less likely than controls to have a “prominent” or “present” paracingulate sulcus and more likely to have an “absent” paracingulate sulcus ($\chi^2 = 6.38, p = 0.041$). OCD = obsessive–compulsive disorder.

| Table 2: Proportion of the cingulate sulcus morphologic classifications of patients with obsessive–compulsive disorder and controls |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Hemisphere     | Group, cingulate sulcus morphology, % | Analysis        |                  |
|                | Control (n = 169) | OCD (n = 110)   | Unpartialled*   | Partialled† |
|                | Continuous | Interrupted | Continuous | Interrupted | $\chi^2$ | p value | $\chi^2$ | p value |
| Left           | 83.4       | 16.6       | 78.2       | 21.8       | 1.20     | 0.27     | 2.05     | 0.15    |
| Right          | 85.8       | 14.2       | 85.5       | 14.5       | 0.01     | 0.94     | 0.01     | 0.93    |

OCD = obsessive–compulsive disorder.
*Likelihood ratio $\chi^2$ test.
†Binary logistic regression (sex and intelligence quotient have been covaried).

| Table 3: Anterior cingulate asymmetry index of patients with obsessive–compulsive disorder and controls |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Group                                           | Asymmetry index, %                              | Analysis                                        |
|                                                | Leftward                                       | Rightward                                      |
|                                                | L >> R (L > R)                                 | L > R (L < R)                                  |
|                                                | Symmetric                                      | L < R (L < R)                                  |
|                                                | L << R (L < R)                                 | L << R (L > R)                                  |
| Control (n = 169)                              | 23.7                                           | 20.7                                           |
|                                                | 37.9                                           | 11.2                                           |
|                                                | 6.5                                            | 1.20                                           |
|                                                | 0.88                                           | 1.07                                           |
| OCD (n = 110)                                  | 19.1                                           | 20.9                                           |
|                                                | 42.7                                           | 10.0                                           |
|                                                | 7.3                                            | 1.07                                           |
|                                                | 0.90                                           |                                                |

L >> R = leftward asymmetry with a difference of 2 categories; L > R = leftward asymmetry with a difference of 1 category; L < R = rightward asymmetry with a difference of 2 categories; L << R = rightward asymmetry with a difference of 1 category; OCD = obsessive–compulsive disorder.
*Likelihood ratio test for trend.
†Polychotomous logistic regression (sex and intelligence quotient have been covaried).
during the brain growth spurt period.\textsuperscript{15} Despite the probably paracingulate sulcus can be identified at 28 weeks' gestation becomes recognizable at 18 weeks' gestation, whereas the determined in a great measure by nongenetic factors.\textsuperscript{46} Moreover, tertiary shallower sulci show greater variability than deeper primary sulci in monozygotic twins, implying that ontogenetically late sulci are less strongly predetermined.\textsuperscript{7,24} Thus, the paracingulate sulcus, as a tertiary sulcus, seems to be under less genetic control than such primary structures as the cingulate sulcus, suggesting that early environmental or epigenetic factors impinging on neurodevelopment may account for the changes observed in patients with OCD.

We speculate from our findings that some psychiatric illnesses can be viewed from within a hierarchical model of neurodevelopmental anomalies. In other words, patients with schizophrenia showed a loss of normal cerebral lateralization due to early neurodevelopmental aberrations, as abnormal brain development in schizophrenia is more likely to be affected by genetic factors compared with other psychiatric disorders. On the other hand, it is probable that patients with OCD experienced normal anatomic cerebral lateralization but that their left paracingulate sulci are reduced, as genetic factors have less influence on the neurodevelopmental anomalies of OCD than on those of schizophrenia. It is known that the left hemisphere matures later than the right in utero.\textsuperscript{4,20} If the left hemisphere were less mature at the time of insult (possibly the second or third trimester) in patients with OCD, the left paracingulate sulcus might show greater differences in subsequent development than the right paracingulate sulcus, as suggested by our study. However, further research supporting this notion is necessary.

As mentioned, abnormal paracingulate or cingulate sulcus morphology has been reported in other psychiatric disorders,\textsuperscript{11,22,26} and an “absent” paracingulate sulcus has been found among many healthy individuals. Thus, an “absent” paracingulate sulcus in the left hemisphere is not exclusive to patients with OCD, implying that morphological anomalies of the ACC, especially the paracingulate sulcus, represent risk factors for several psychiatric illnesses rather than for any specific diagnosis.

Cortical folding has multifactorial causes, including neuronal differentiation and synaptogenesis,\textsuperscript{23} and is affected by neural connectivity (i.e., axonal connections among different brain regions).\textsuperscript{42,83} Developmentally mediated network dysplasia has been suggested to underpin OCD.\textsuperscript{83} Thus, it is possible that the ACC morphologic anomalies in patients with OCD reflect disturbed neuronal connectivity occurring early in life. Researchers have found that normal variations in paracingulate sulcus morphology were associated with verbal and nonverbal executive tasks,\textsuperscript{7,25} and that paracingulate sulcus asymmetry patterns were related to individual differences in temperament.\textsuperscript{19} It has been reported that patients with OCD had impaired executive function\textsuperscript{19} and had characteristic patterns of temperament and character compared with healthy controls.\textsuperscript{7} Thus, we need further studies to investigate whether the ACC morphologic anomalies in patients with OCD are associated with impaired executive function and distinct patterns of temperament.

Limitations

There are several limitations to our study. First, we obtained the MRI scans from 2 different scanners. However, unlike volumetric measures, categorical measures of gross morphology have been shown to be robust to minor differences between scanners,\textsuperscript{19} and there were no significant differences between the 2 scanners in the paracingulate sulcus classifications. In our previous study using the same 2 scanners, we also observed no differences in the pituitary volume of controls between MRI scanners.\textsuperscript{20} Our study was restricted to 1 specific brain region, and we did not calculate cerebral fissurization. However, previous studies have reported that paracingulate/cingulate sulcus variations were independent of global folding patterns,\textsuperscript{14,20} suggesting that our results were not a consequence of more generalized abnormalities (i.e., differences in folding across the entire cerebral hemisphere). In addition, the higher ratio of male to female patients with OCD might not have influenced our results since the left paracingulate sulcus is more common among men\textsuperscript{11,13} and sex was controlled as a covariate.

Conclusion

Our findings support previous neuroimaging studies suggesting that the ACC is involved in the pathophysiology of OCD and imply that a subtle change results in reduced cortical folding of the left ACC during the early neurodevelopment of those with OCD. We postulate that neurodevelopmental anomalies in OCD are less severe than those in schizophrenia since cingulate sulcus continuity and normal cerebral asymmetry were preserved in OCD. Nonetheless, the extent to which these anomalies contribute to the pathogenesis of OCD remains unclear. Further studies that could reveal the role of these anomalies in its pathophysiology are mandated.

Acknowledgements: This work was supported by Cognitive Neuroscience Program of the Korean Ministry of Science and Technology (M10644020003-08N4402-00310).

Competing interests: None declared.

Contributors: Drs. Shim, Kang and Kwon designed the study. Mr. W.H. Jung, Ms. Park and Drs. J.S. Choi, M.H. Jung, Jang, C.H. Choi and Kang acquired the data, which Dr. Shim, Mr. W.H. Jung and Ms. Park analyzed. Dr. Shim wrote the article, which all other authors reviewed. All authors gave final approval for publication.

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