Ventricle-to-Brain Ratio and Symptoms at the Onset of First-Break Schizophrenia

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Abstract

Ventricle-to-brain ratio (VBR) was measured from the computed tomographic (CT) scans of 33 very recent-onset psychotic patients. Illness severity and positive and negative symptoms were also assessed in 21 of these patients with schizophreniform disorder. Forty-five neurology patients served as controls. Analyses revealed no significant differences between the VBR of the psychotic group as a whole, the schizophreniform subgroup, the affective psychotic subgroup, and the controls. Control subjects with a neurological diagnosis of vertigo or syncope had significantly higher VBR than the remainder of the control group and the psychotic group. When the psychotic group was compared to the control group minus those controls with syncope or vertigo, the psychotic group had significantly higher VBR. The schizophreniform subgroup also had significantly higher VBR than the control group minus subjects with vertigo or syncope. In the schizophreniform subgroup, positive symptoms and illness severity were associated with smaller VBR. There was no association between negative symptoms and VBR.

The application of noninvasive neuroimaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) to the study of the neuroanatomy of the major psychoses has made possible a great deal of research. The most consistent finding of this research has been lateral ventriculomegaly in schizophrenia. This finding is usually expressed as the ventricle-to-brain ratio (VBR) (Shelton and Weinberger 1986; Farmer et al. 1987). Increased VBR has also been reported in psychotic patients with affective disorders (Nasrallah et al. 1989; Raz and Raz 1990). However, this research suggests that ventriculomegaly and other neuroimaging abnormalities characterize only a subpopulation of both schizophrenic and affective disordered patients (Raz and Raz 1990). Among schizophrenic patients, it has been suggested that the negative symptom syndrome may be associated with increased VBR (Andreasen et al. 1982a, 1982b). Also, the relationship between anatomical differences and clinical variables, such as age at onset, course, severity, symptom manifestations, and prognosis, remains unclear. This study examined the relationship between VBR, diagnosis, and symptoms in a group of very-recent-onset psychotic patients.

Current evidence favors a nonprogressive etiology for the ventriculomegaly associated with psychotic disorders. This probably represents aplasia or hypoplasia (Nasrallah et al. 1986; Illowsky et al. 1988; Vita et al. 1988; Zipursky et al. 1988). However, conflicting evidence of a progressive defect has been reported (Kemali et al. 1989; Schwarzkopf et al. 1990; Woods et al. 1990). In the schizophrenic subpopulation, further support for a dysgenesis is inferred from studies showing a defect observable early in the course of the disorder (Nyback et al. 1982; Weinberger et al. 1982; Schulz et al. 1983; Owens et al. 1985; Turner et al. 1986; Scottish Schizophrenia Research Group et al. 1989; Bogerts et al. 1990), although this finding has not been universal either (Benes et al. 1982). To date little has been published on the neuroimaging of...
early or first-break affective psychoses. Early-course studies have been flawed by problems with case definition, control group selection, and small sample size.

In a disease of long duration such as schizophrenia, the terms "acute," "early," and "first episode" are used with some imprecision. In the relevant studies, the mean durations of illness reported were 1.4 years (Bogerts et al. 1990), 4.5 years (Benes et al. 1982), 13 months (Schulz et al. 1983), and 9+ months (Turner et al. 1986); mean lengths of illness were not reported by Weinberger et al. (1982), Nyback et al. (1982), Owens et al. (1985), and the Scottish Schizophrenia Research Group et al. (1989). Studies by Weinberger and colleagues (1982) and Owens and colleagues (1985) did specify the diagnosis of schizophreniform disorder, implying a duration of symptoms of fewer than 6 months. These studies are neither prospective nor consistent in finding increased VBR. It is unclear from the results of these studies that ventriculomegaly antedates the disorder.

The issue of control group composition and its influence on the reporting of ventricular enlargement has been studied by several researchers (Andreasen et al. 1982a; Maser and Keith 1983; Smith and Iacono 1986; Lewis 1990). There are conflicting opinions as to how much influence selection of medical or neurological controls has on mean VBR for these control groups and, consequently, on the probability of finding ventriculomegaly in psychotic populations. However, it is clear that there is considerable variability in VBR in healthy populations.

Other demographic variables that may influence VBR include age (Barron et al. 1976; Zatz and Jernigan 1983), social class (Pearson et al. 1985), height, ethnicity (Nimgaonkar et al. 1988), education (DeMyer et al. 1988), and sex (Andreasen et al. 1990; Flaum et al. 1990).

The current study has successfully captured a group of very recent-onset, first-break psychotic patients. In this study of a high-school-educated, physically healthy, employed, and diagnostically heterogeneous group of psychotic patients, we examined the relationship between VBR and diagnosis at the onset of psychotic symptoms. We also examined the relationship between symptom severity, positive and negative symptoms, and VBR in a subgroup of schizophreniform patients.

**Method**

**Patient Sample.** A total of 33 first-break psychotic patients participated in this study. These patients were enrolled in the study an average of 3.8 days after their initial presentation with psychotic symptoms (range = 1–14 days). Of the 33 patients, 21 were direct admissions to the Eisenhower Army Medical Center (EAMC) Inpatient Psychiatry Service on the day of presentation. The 12 patients transferred from other facilities were admitted to the center an average of 9 days after initial presentation (range = 1–14 days).

All patients admitted to the service during a 30-month period with a diagnosis of psychotic disorder were screened. Patients included in the study were between the ages of 18 and 30 years and were active duty military. Patients also had normal CT scans and normal electroencephalograms (EEGs). Patients were excluded from the study if they had a history of psychiatric problems or alcohol or drug dependence or abuse (experimental drug use and social use of alcohol were not exclusionary). Other exclusionary criteria were a positive drug screen on admission, a significant medical or neurological illness, or a history of head trauma resulting in loss of consciousness for more than 1 minute. Finally, an initial clinical screening was performed using the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962) to establish the presence of a gross psychosis. A score of 30 or greater was used to identify potential study patients.

**Control Sample.** A total of 45 neurological patients served as the control group. These subjects were all young (18–32 years), healthy, working, and active duty military. Their neurological, physical, and laboratory examinations were all normal, and all continued to perform their military duties after their neurological evaluation. This patient group was selected because a CT scan was included as part of their neurological workup.

**Procedure.** All patients were admitted to the general psychiatry inpatient service of EAMC. After an initial screening examination by the admitting physician, the research team was alerted. A member of the research team performed a second screening exam to determine eligibility for inclusion in the protocol and obtained patient consent. If the patient was medication free at that time, a complete clinical interview was conducted by a pair of clinicians from the research team. Most patients had received no neuroleptic treatment before their admission at EAMC. Those patients who had received psychotropic medications before their transfer to EAMC had a 96-hour neuroleptic washout or a
The Clinical Global Impression scale (CGI; Guy 1976) was used to provide a single global severity of illness score on a scale of 1 (least severe) to 7 (most severe). The modified 25-item Schedule for the Assessment of Negative Symptoms (SANS; Andreasen 1982) was used to identify negative symptoms. This instrument provides a measurement of five different symptom complexes: alogia, anhedonia, affective flattening, avolition, and attention. Each item is scored on a 6-point severity scale (0 to 5), with 5 representing the most severe. Five items are global items measuring the overall severity of the five symptom complexes. The SANS may be used to yield two measurements of overall severity of negative symptoms. One overall score, the summary score, is the sum of the five global items that relate to each of the five different symptom complexes. The composite score is the sum of all 25 items on the scale.

All rating scales were completed independently by two raters based on the same clinical interview. The interview was then discussed to ensure a common observational data base, and raters modified their ratings as indicated by the consensus-based observations. Remaining differences between raters were handled by using the average score for each item to compute the summary (SANS) and composite (BPRS and SANS) scores.

In addition, a complete neurological examination, CT scan of the head, and EEG were obtained to establish eligibility to participate. The treating physicians were blind to the CT and EEG results.

Final diagnoses were drawn from the inpatient record at the time of discharge. Because patients with psychotic illnesses must be medically discharged from military service, most patients had extended inpatient stays (3-4 months) while waiting for their discharges. This extended observation and treatment period allowed ample opportunity to establish a firm diagnosis. All diagnoses of schizophreniform disorder were established using DSM-III-R (American Psychiatric Association 1987) criteria based on consensus between the treating resident and the supervising staff psychiatrist, neither of whom was involved in the research ratings. Furthermore, as part of the medical discharge process, a medical board convened to review diagnosis. This provided further confirmation of the final diagnosis of schizophreniform disorder.

Computed Tomography. Patients were scanned using a General Electric 9800 scanner. All scans were axial and scanned slices were 10 mm thick. Patient scanning was accomplished during the first 2 weeks of hospitalization in most cases. In the absence of other cerebral pathology, patients were not excluded solely because of a radiologic report of enlarged ventricles. Otherwise only patients with radiological diagnoses of "normal CT" were included.


computerized image analysis system. Lighting was maximized and inhomogeneities of the background were referenced for correction against each image. Scans were digitized with a DAGE 68 camera interfaced to an IBM-AT personal computer via an expansion chassis. The x-ray films were digitized 16 times and the average transmission value for each pixel element was calculated. The resultant image was plotted on a monitor, color coded, and selectively contrast enhanced to portray the brain and cerebrospinal fluid transmission values. The final magnification for each image was 2X with a resolution (i.e., the length of the image as seen on the monitor divided by the number of pixels across the measured axis) of 0.31 mm. Because the final experimental variable was expressed as a ratio of two areas, measurements were not calibrated against the horizontal or vertical metric scale of the CT. Areas were computed using the method described by Press (1956). One level per scan was measured twice and the average value computed for the purpose of this investigation. The anatomical level was defined as that having the largest extension of ventricle; it usually lay under the centrum semiovale.

Results

The characteristics of the patient and control groups are presented in Table 1. The patient group consisted of 33 first-break psychotic patients, 21 of
Table 1. Demographic characteristics of the patient and control samples

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (n = 33)</th>
<th>Controls (n = 45)</th>
<th>Controls (minus)¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD)</td>
<td>21.1 (2.9)</td>
<td>25.1 (3.8)</td>
<td>25.4 (3.7)</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>73</td>
<td>67</td>
<td>68</td>
</tr>
<tr>
<td>Rank (% enlisted)</td>
<td>94</td>
<td>96</td>
<td>97</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>53</td>
<td>50</td>
<td>47</td>
</tr>
<tr>
<td>Black</td>
<td>31</td>
<td>43</td>
<td>50</td>
</tr>
<tr>
<td>Asian</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Hispanic</td>
<td>13</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

¹Control group excluding patients with vertigo or syncope.

whom were diagnosed with schizophréniform disorder. Diagnoses of the patient group are listed in table 2. The mean (standard deviation [SD]) age for the patient group was 21.09 (2.90) years; 73 percent were male, and 94 percent were enlisted soldiers. The diagnoses of the 45 neurology outpatients in the control group are reported in table 3. The mean (SD) age for the control group was 25.13 (3.75) years. Seventy-one percent of the control group were male, and 96 percent were enlisted soldiers. There were no differences between the groups in racial composition (table 1). Because the patient and control groups were matched for military rank, it can be inferred that the two groups were of similar educational background and socioeconomic status. Although the age difference between the control group and the patient group was significant (F = 26.63; df = 1.76; p < 0.001), a multiple regression analysis revealed that age did not account for a significant amount of the variance in VBR. Although some researchers have reported that gender is related to VBR, in this sample sex did not account for a significant amount of variance in VBR.

Table 2. Diagnoses of patient sample

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophréniform</td>
<td>21</td>
</tr>
<tr>
<td>Bipolar—manic</td>
<td>7</td>
</tr>
<tr>
<td>Brief reactive</td>
<td>2</td>
</tr>
<tr>
<td>Delusional</td>
<td>1</td>
</tr>
<tr>
<td>Schizoaffective</td>
<td>1</td>
</tr>
<tr>
<td>Major depression</td>
<td></td>
</tr>
<tr>
<td>with psychotic features</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>33</td>
</tr>
</tbody>
</table>

Table 3. Neurological diagnoses of controls

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine</td>
<td>18</td>
</tr>
<tr>
<td>Other headache</td>
<td>8</td>
</tr>
<tr>
<td>Syncope</td>
<td>6</td>
</tr>
<tr>
<td>Vertigo</td>
<td>2</td>
</tr>
<tr>
<td>Miscellaneous¹</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>45</td>
</tr>
</tbody>
</table>

¹Anosmia, hypoparathyroidism, amnesia, paresthesia, facial pain, back pain, myopathy, pseudoseizure, fugue, conversion, and dizziness.

VBR and Diagnosis. In a comparison of the VBR of patients to that of controls, it was predicted that the VBR would be greater in the psychotic group than in the control group. A one-way analysis of variance (ANOVA) indicated no significant difference between the VBR of patients and controls. However, the means for these groups were in the expected direction (table 4).

Because much of the work relating ventricular enlargement to psychosis has focused on schizophrenic patients, we divided our experimental group into schizophréniform patients and patients with other diagnoses. A one-way ANOVA with orthogonal contrasts was used to compare VBR between three groups (schizophréniform, all other diagnoses, and controls). Again, there were no significant differences between the three groups, but the means were in the expected direction (table 4). Furthermore, our findings corroborate those of Weinberger and colleagues (1982) and Owens and colleagues (1985) in demonstrating that VBR of affective psychotic patients lies between that of schizophréniform patients and controls.

The mean VBR for our control group appeared larger than the VBR reported for medical controls in other studies, so we reviewed the VBR of the control subjects by diagnosis. Because the VBR of the vertigo/syncope patients was unusually large (mean = 9.3, SD = 2.49), we decided to reanalyze the data, treating these subjects as a separate group. The remaining control subjects were redesignated the "control group (minus)." Again, a one-way ANOVA with orthogonal contrasts was performed to evaluate differences between the schizophréniform group, the group of all other psychotic patients, the control group
Table 4. Ventricle-to-brain ratios (VBR)

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>33</td>
<td>7.9</td>
<td>2.5</td>
</tr>
<tr>
<td>Schizophreniform only</td>
<td>21</td>
<td>8.1</td>
<td>2.7</td>
</tr>
<tr>
<td>All other (^1)</td>
<td>12</td>
<td>7.3</td>
<td>2.3</td>
</tr>
<tr>
<td>Affective only</td>
<td>8</td>
<td>7.6</td>
<td>2.7</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>45</td>
<td>7.3</td>
<td>2.3</td>
</tr>
<tr>
<td>Syncope/vertigo</td>
<td>8</td>
<td>9.3</td>
<td>2.5</td>
</tr>
<tr>
<td>Control group (minus)(^2)</td>
<td>37</td>
<td>6.8</td>
<td>2.1</td>
</tr>
</tbody>
</table>

Note.—SD = standard deviation.

\(^1\)All patients minus schizophreniform patients.

\(^2\)Control group excluding patients with syncope or vertigo.

Schizophreniform Patients and Symptomatology. Because of previously hypothesized relationships between VBR and positive and negative symptoms in schizophrenic patients, analyses were directed toward examining the relationship between psychotic symptoms and VBR in the schizophreniform patients only.

Of the 21 schizophreniform patients included in this study, 15 were male and 6 were female. Fifty-five percent of the sample was white, 20 percent was black, another 20 percent was Hispanic, and the remaining 5 percent was Asian. The mean (SD) age of the group was 21.19 (2.89), and subjects' ages ranged from 18 to 28. The mean (SD) VBR was 8.08 (2.69).

Data analyses first examined the relationship between negative symptoms and VBR. The mean (SD) composite SANS score for this group was 49.67 (19.94). A series of separate regression analyses was performed on each of the five subscales, the summary score, and the composite score to test for the contribution of VBR to negative symptoms. The VBR was entered as the predictor variable for each of the dependent measures. Regression analyses revealed that VBR was not a major factor in negative symptom scores for this group of patients. The VBR did not account for significant amounts of variance for the subscale scores or for either of the two overall scores.

In a similar analysis designed to explore the relationship between VBR and positive symptoms, VBR accounted for approximately 14 percent of the variance associated with the BPRS and the CGI. In two separate equations, the VBR was entered as the predictor of the BPRS score and the CGI score. The first analysis revealed that the VBR accounted for approximately 15 percent of the variance associated with the BPRS score (\(F = 3.46; df = 1.19; p < 0.08\)). The BVR and BPRS were negatively correlated. The VBR did not account for a significant amount of variance in symptom severity as measured by the CGI scale. The mean (SD) BPRS score was 47.79 (9.98). The mean (SD) CGI score was 4.69 (1.05). The correlation between the SANS and BPRS was 0.48.

Discussion

Results of the present study further support the notion that ventriculomegaly is present at the onset of psychotic symptoms. In this population, VBR was larger in the schizophreniform patients compared to controls (minus). Although the differences were not significant, affective psychotic VBR lay between the schizophreniform VBR and the control VBR. In schizophreniform patients, higher VBR was not associated with greater negative symptoms. Schizophreniform patients with lower VBR, however, had marginally greater positive symptoms and higher symptom severity scores on the BPRS.

The sample of subjects evaluated in this study is unique in that they were all active duty military. This aspect of the study is important for at least two reasons. First, we know that the psychotic symptoms were
acute and of recent onset; second, we know that the patients had good premorbid functioning.

Because of the nature of military service, as soon as symptoms are identifiable in the daily work setting, service members are referred for medical treatment. Unlike the civilian world, in which neither work nor medical treatment are mandatory and treatment is often delayed, this aspect of military life made it possible for us to identify a group of very-recent-onset, first-break psychotic patients. In fact, these subjects were initially evaluated for this study an average of 3.8 days following the onset of observable symptoms.

Current theorists favor the view that the ventriculomegaly seen in conjunction with psychosis is a result of a hypoplastic defect that is stable over time and is independent of the progression of psychosis. However, this theory is based primarily on research that allows for rather extensive histories of psychiatric symptomatology before study (i.e., Benes et al. 1982; Nyback et al. 1982; Weinberger et al. 1982; Schulz et al. 1983; Owens et al. 1985; Turner et al. 1986; Scottish Schizophrenia Research Group et al. 1989; Bogerts et al. 1990). The present sample was scanned very early in the psychotic process and tends to support the hypoplasia theory. However, because this study is not prospective, we cannot rule out an acute atrophic process that is rapidly progressive but brief in duration, begins before development of psychotic symptoms in susceptible individuals, and terminates in psychosis.

Unlike many of the subjects in other samples, the subjects in this group were able to function effectively in society before their first psychotic episode. We know that our subjects who were new recruits were able to pass basic screening done at induction. These patients all volunteered for active duty military service, met induction criteria, and passed initial physical and mental screening tests. Military induction standards have been higher than at any time in the past, requiring among other things a high school diploma or its equivalent. Individuals with discoverable histories of criminal conduct, psychiatric hospitalization, or significant substance abuse have been excluded, and the induced population has been physically healthy, not obese, and physically fit relative to the general population. We know that those subjects who had been in the service for some time were able to maintain adequate job performance before referral. Many had completed basic and occupational skill training and were functioning in a regular duty assignment. For these reasons, we can classify our subjects as a "healthy" group of psychotic patients. Persons with childhood or early adolescent onset of symptoms were excluded. This group would also be more likely to exclude those patients with poor premorbid functioning, especially impaired cognitive functioning, poor scholastic achievement, and poor social adaptation.

Because severity of illness (DeLisi et al. 1983; Pandurangi et al. 1988) and poor premorbid adjustment (Weinberger et al. 1980; Pearlson et al. 1985; Williams et al. 1985; Pandurangi et al. 1988) have been associated with higher VBR, one might expect a lower prevalence of increased VBR in our military population. The finding of increased VBR in our group therefore assumes additional significance.

The issue of control group composition and its influence on reporting of ventricular enlargement has been debated by others (Andreasen and Olsen 1982; Maser and Keith 1983; Smith and Iacono 1986; Raz et al. 1988; Smith et al. 1988; Lewis 1990; Raz and Raz 1990). This issue is important for the present study as well. Opinions differ about how much influence selection of medical or neurological controls has on mean VBR for these control groups and consequently on the probability of finding ventriculomegaly in psychotic populations. Smith and colleagues (1988) have clearly expressed the potential perils of control selection. The authors demonstrated that selection of control group strongly influences the possibility of finding increased VBR in the experimental group. In their study, medical controls were found to have smaller ventricles than non-patient volunteer controls, which increased the likelihood of finding ventriculomegaly in psychotic study populations. Other authors (Maser and Keith 1983) have contended that medical controls have larger VBR than volunteers. Still others (Dennert and Andreasen 1983) have found no difference between normal and medical controls. Raz and colleagues (1988), in their meta-analysis, found similar effect sizes in studies using healthy volunteer, medical, neurological, and psychiatric controls. This debate suggests that there is considerable variability in VBR in "healthy" populations.

Because CT scans were included as part of their routine care, neurology patients were chosen as control subjects in this study. Only neurology patients with normal neurological, physical, and laboratory examinations were included. We did not exclude patients on the basis of their diagnosis; however, after examining the data it became clear that the VBR of the syncope/vertigo subjects were unusually large. The exact sig-
nificance of this finding is unclear and remains a question for future studies: perhaps subtle brain changes caused the symptoms. However, vertigo/syncope patients will be excluded from our control group in the future.

Although other research has suggested a positive association between VBR and negative symptoms in schizophrenic patients, we found no such association for patients with schizophreniform disorder. It is possible that no such association exists for schizophreniform patients. However, the unique nature of our sample may have contributed to this finding. The classical negative symptom syndrome is associated with insidious onset and poor premorbid functioning, including impaired cognitive functioning, poor scholastic achievement, and poor social adaptation. Also, the psychoses of our patients were typically abrupt in onset as opposed to the insidious onset hypothesized for the negative symptom syndrome. Our clinical impression is that, based on symptom presentation alone, this patient population was predominantly composed of the positive and mixed varieties described by Andreasen and Olsen (1982). It is possible, therefore, that our failure to find an association between higher VBR and negative symptoms was due to the underrepresentation of the classical negative symptom syndrome in this population.

However, these data did not support the notion of a continuum manifested by rising negative symptom scores associated with rising VBR. Our data would argue indirectly that, if a negative syndrome exists and is associated with large VBR, then it is a separate and distinct subgroup and not at the opposite end of a continuum shared with the positive symptom syndrome. This conclusion supports that of Crow (1985), who argues for the existence of discrete schizophrenia subtypes and contradicts the continuum hypothesis of Andreasen (1985) and Andreasen and Olsen (1982). It is worth noting that of the three patients in this study whose VBR was greater than 2 SD above the control mean, only one had high negative symptoms (SANS composite scores of 66, 15.5, and 13).

Our finding that lower VBR was also associated with a more floridly symptomatic presentation as measured by the BPRS provides additional validation of Crow’s Type I concept of a florid, hyperdopaminergic psychotic illness without a significant structural component. The Type I concept also includes a dimension of treatment responsivity that will be tested in the future.

In conclusion, this work provides a preliminary look at a unique population of very-recent-onset psychotic patients. As the study progresses, more subjects will be added to each group. Also, when resources and equipment become available, MRI data will be included as well. In this way, we will collect more accurate measures of discrete brain substructures. Finally, we hope to follow these subjects longitudinally as they seek medical care through the Department of Veterans Affairs.

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