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Clinical Study

Cerebral arteriostenosis associated with elevated serum-immunoglobulin E level in young adults without risk factors for ischemic stroke: A possible manifestation of cerebral vasculitis?

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ABSTRACT

We report a series of young adults with symptomatic cerebral arteriostenosis characterized by elevated serum immunoglobulin (Ig) E levels. All patients had no definite risk factors for cerebral vascular diseases. The clinical data of 26 young adults (age 18–50 years) with ischemic stroke, characterized only by increased serum IgE levels and without risk factors for cerebral vascular disease, were retrospectively reviewed. Arteriostenosis was surveyed and followed-up by digital subtraction angiography (DSA), and the stenosis rate was estimated using the warfarin–aspirin symptomatic intracranial disease technique. All patients were treated with corticosteroids according to the common strategy for vasculitis. There was no recurrent stroke during follow-up. The mean degree of stenosis before and after treatment was $69.3 \pm 29.8\%$ and $47.9 \pm 45.1\%$, respectively. The difference of stenosis rates between initial and follow-up DSA evaluation was significant using a paired samples test (21.31 ± 26.88 , 95% confidence interval [CI] 13.58–29.03, $t = 5.55$, $p < 0.001$). Kaplan–Meier survival analysis revealed that the 13-month cumulative improved lesion rate was $40.3 \pm 8.7\%$. This remained the same at 18 months. The mean time to lesion improvement was 12.58 ± 0.96 months (95% CI 10.70–14.46) and median time was 13 ± 3.88 months (95% CI 5.39–20.61). To our knowledge, cerebral arteriostenosis with only elevated IgE serum levels has not been reported. Our data showed that corticosteroid treatment can achieve clinical and artery improvement. This suggests that the cerebral arteriostenosis seen in our study might be caused by some specific type of vessel inflammation.

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1. Introduction

Vasculitis, characterized by inflammation of blood vessel walls, can result in vessel wall destruction with hemorrhage, aneurysm formation, infarction, or stenosis caused by intimal hyperplasia. It can be a primary process with unknown cause, or a result of a wide range of disorders. There are still critical gaps in the diagnosis and treatment of vasculitis. A diagnosis of vasculitis is based on clinical features, laboratory tests, radiographic abnormalities, and histologic findings. However, the diagnosis of vasculitis is a great medical challenge due to the unknown etiology and pathogenesis of most vasculitic disorders, as well as their elusive clinical and pathologic characteristics.¹ In some cases, patients with no clinical or laboratory signs of inflammation are clinically diagnosed with

vasculitis because of their responsiveness to immunosuppressive and cytotoxic agents.

Immunoglobulin (Ig) E, a well-known mediator of allergy, binds to the Fc receptor on mast cells or basophil leading to a type I allergic response. In addition, IgE can also cause platelet activation and aggregation, and arterial smooth muscle hyperplasia.^{2,3} Elevated IgE levels have been found in some types of vasculitis although the precise role of IgE in the pathogenesis of vasculitis remains elusive. In recent years, increased levels of serum IgE have also been found in patients with cardiovascular or cerebrovascular diseases. Some studies suggested that IgE may function as a risk factor for coronary disease.^{4,5} Moreover, an elevated IgE serum level has been found in patients with cerebral infarction during the acute stage.⁶

Here we describe a series of 26 patients with possible vasculitis characterized by a persistent high level of serum IgE. All patients had symptoms associated with arterial stenosis. Interestingly, we failed to find any other abnormal parameters indicative of inflammation or atherosclerosis. Therefore, all these patients did not

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meet the diagnostic criteria for vasculitis according to the Chapel Hill Consensus Conference.

2. Patients and methods

Between September 2006 and April 2011, 26 consecutive patients (16 men and 10 women) with an increased serum IgE level were retrospectively reviewed. Demographic characteristics, conventional risk factors for ischemic stroke, lesion variables, autoimmune antibodies, qualifying events at admittance, inflammatory markers, follow-up angiographic findings, treatments and clinical outcomes were documented in the Nanjing Stroke Registry Program.⁷ The clinical and angiographic data of these patients is summarized in Table 1. Patient age ranged from 19 to 45 years with a

mean and midmean of 37.4 and 40.5 years, respectively. All patients were capable of average physical activity and were young adults without hypertension, heart disease, diabetes, hyperlipemia, cigarette smoking, alcohol abuse, obesity or hyperhomocysteinemia, and were not taking oral contraceptives. Autoimmune antibodies and immunoglobulin (IgA, IgG and IgM) concentrations were normal in all patients. Allergy analysis using ImmunoCAP (Pharmacia Diagnostics, Uppsala, Sweden) showed that two of the 26 were hypersensitive to dust mites. There was no evidence of parasite or microorganism infection in any patient.

The cerebral arteries were evaluated by cerebral digital subtraction angiography (DSA). Intracranial artery stenosis was defined as a degree of stenosis $\geq 30\%$. Low, medium and severe stenosis were defined as a stenotic rate of 30–49%, 50–69% and 70–99%,

Table 1
Characteristics of patients treated with corticosteroids for cerebral artery stenosis and their angiographic results

Before corticosteroid treatment					After corticosteroid treatment	
C/S/A	IgE	Presenting symptom	CT/MRI findings	Angiographic findings pretreatment	IgE	Angiographic findings
1/F/45	184	Dizziness	No infarct	LCCA (100%), RVA (80%), RECA (50%), RCCA (30%), RICA (30%), RSCA (30%)	375	LCCA (30%), RVA (0%), RECA (0%), RCCA (30%), RICA (0%), RSCA (0%)
2/F/45	589	Dizziness	No infarct	LMCA (99%)	327	LMCA (100%)
3/F/43	288	Dizziness	No infarct	LICA (90%), LMCA (70%), RICA (30%)	302	LICA (50%), LMCA (30%), RICA (0%)
4/F/44	163	Dizziness	No infarct	LVA (30%)	183	LVA (0%)
5/F/29	443	Dizziness	No infarct	RSCA (80%), RVA (70%), LCCA (70%), RMCA (30%)	514	RSCA (80%), LCCA (40%), RVA (0%), RMCA (0%)
6/F/43	248	Dizziness	No infarct	RMCA (40%)	257	RMCA (0%)
7/F/30	173	Dizziness, headache	No infarct	RMCA (100%)	217	RMCA (100%)
8/M/45	225	Syncope	Left cerebellar infarcts	RMCA (100%), LMCA (100%)	279	RMCA (100%), LMCA (100%)
9/M/41	263	Anterior circulation TIA	No infarct	LMCA (40%), RICA (40%), LICA (30%)	316	LMCA (0%), RICA (0%), LICA (0%)
10/M/37	373	Anterior circulation TIA	No infarct	LMCA (30%)	385	LMCA (0%)
11/M/26	221	Anterior circulation TIA	No infarct	RACA (100%), RICA C7 (60%)	175	RACA (100%), RICA C7 (60%)
12/F/32	658	Anterior circulation TIA	No infarct	RMCA (100%), LMCA (100%)	574	RMCA (100%), LMCA (100%)
13/M/31	297	Anterior circulation TIA	No infarct	RMCA (70%), LMCA (30%)	210	RMCA (70%), LMCA (0%)
14/M/41	220	Anterior circulation TIA	Right cerebellar infarcts	RICA (100%), RPCA (100%), LICA (100%), LCCA (50%)	257	RICA (100%), RPCA (100%), LICA (100%), LCCA (50%)
15/M/44	239	Anterior circulation TIA	Bilateral cerebellar infarcts	RICA (100%), RACA (100%), LMCA (80%)	210	RICA (100%), RACA (100%), LMCA (50%)
16/M/31	172	Anterior circulation stroke	Left cerebellar infarcts	LMCA (100%)	NA	NA
17/F/41	592	Anterior circulation stroke	Right cerebellar infarcts	RICA (100%)	562	RICA (100%), RPCA (60%)
18/M/37	327	Anterior circulation stroke	Right cerebellar infarcts	RICA (100%)	295	RICA (100%)
19/M/40	214	Anterior circulation stroke	Right cerebellar infarcts	RICA (95%)	232	RICA (100%)
20/M/37	164	Anterior circulation stroke	Right cerebellar infarcts	RMCA (100%)	189	RMCA (100%)
21/M/35	962	Anterior circulation stroke	Right cerebellar infarcts	RMCA (80%), RICA (60%)	549	RICA (30%), RMCA (0%)
22/M/44	318	Anterior circulation stroke	Right cerebellar infarcts	RMCA (30%)	329	RMCA (0%)
23/M/45	658	Anterior circulation stroke	Bilateral cerebellar infarcts	RMCA (99%)	633	RMCA (99%)
24/M/41	186	Posterior circulation stroke	Left brain stem infarct	RVA V3 (60%), LVA V3 (50%)	236	RVA (0%), LVA (0%)
25/F/19	485	Posterior circulation stroke	Right brain stem infarct	BA (100%)	593	BA (100%)
26/M/26	857	Posterior circulation stroke	Pontine, cerebellum, occipital infarcts	BA (100%)	NA	NA

A = age (years), BA = basilar artery, C = code, F = female, IgE = immunoglobulin E (international units/ml), LCCA = left common carotid artery, LICA = left internal carotid artery, LMCA = left middle cerebral artery, LVA = left vertebral artery, M = male, NA = not available, RCCA = right common carotid artery, RECA = right external carotid artery, RICA = right internal carotid artery, RMCA = right middle cerebral artery, RSCA = right subclavian artery, RVA = right vertebral artery, S = sex, TIA = transient ischemic attack.

respectively. In the case of tandem stenotic lesions the most severe stenotic lesion was used. All patients were treated with corticosteroids (dexamethasone and/or prednisone) for more than 3 months. Improvement of cerebral arterial stenosis was defined as the degree of stenosis decreasing by $\geq 20\%$.

2.1. Statistical analysis

Continuous data are expressed as mean $\pm$ standard deviation, and categorical data are presented as the count (percentage). Paired Student's *t*-test was performed to compare stenotic rates

before and after corticosteroid therapy. Kaplan–Meier analysis was performed to detect the cumulative improved lesion rate. $p < 0.05$ was considered statistically significant. All analyses were performed with the Statistical Program for the Social Sciences volume 13.0 (SPSS Inc., Chicago, Illinois, USA).

3. Results

As shown in Table 1, 26 patients with baseline IgE levels above 150 international units/mL were enrolled in this study. All patients

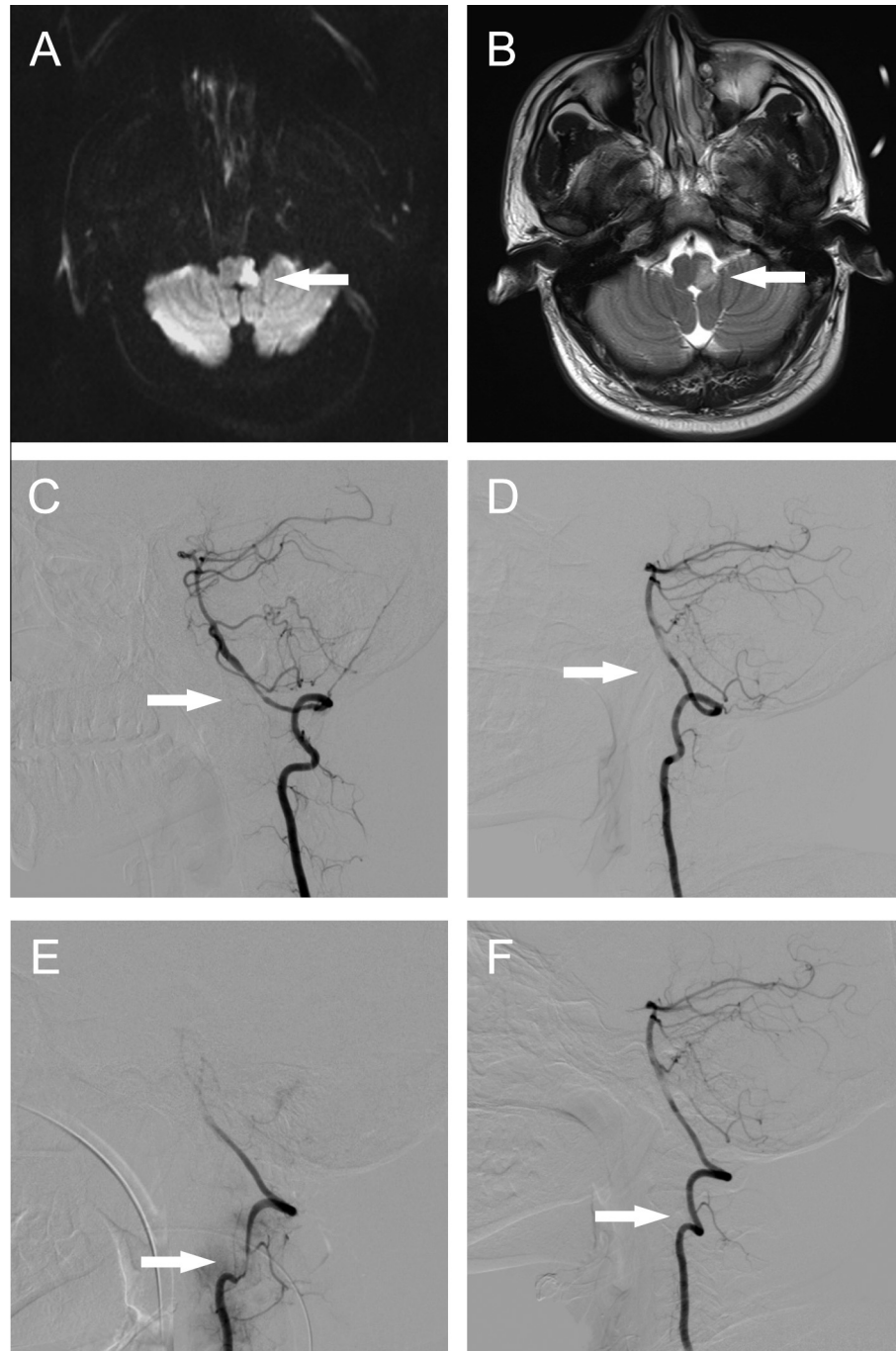


Fig. 1. Patient 24 (A) axial diffusion-weighted MRI and (B) axial T2-weighted MRI showing infarction in the left medulla. Digital subtraction angiograms showing severe vertebral artery origin stenosis before treatment (C, E), and no stenosis after corticosteroid treatment at follow-up 6 months later (D, F).

had symptomatic transient ischemic attack, stroke, syncope, or dizziness. Forty-nine stenosed arteries were detected before treatment, among which 15 showed low stenosis, eight had medium stenosis, and 26 had severe stenosis. In one patient (Patient 24), who had symptoms attributable to posterior circulation infarction (Fig. 1A, B), DSA showed medium stenosis (>50%) in the vertebral arteries (Fig. 1C, E). After corticosteroid treatment, the vertebral arteries completely recovered (0% stenosis; Fig. 1D, F) with improved symptoms. Without corticosteroid treatment, another patient (Patient 23) with no cerebral artery stenosis after his first stroke (Fig. 2A) had developed to right middle cerebral artery (RMCA) severe stenosis after a recurrent stroke (Fig. 2C). DSA showed 99% stenosis of the RMCA (Fig. 2F) with recurrent stroke (Fig. 2D) before he was admitted to our hospital. In our study, corticosteroid treatment decreased the mean stenotic rates. In addition to the two patients described above, the other 24 patients also showed sensitivity to corticosteroid therapy.

One female patient (3.8%, 1/26) was lost to follow-up. Only one death (3.8%, 1/26) occurred in a male patient and was attributed to serious multiple strokes with “top of the basilar” syndrome. The rest of the patients ($n = 24$) had clinical and DSA follow-up. No recurrent stroke was seen during clinical follow-up at a mean and median time of 18.4 ± 16.1 and 11.5 months, respectively (range, 4–55 months).

Twenty-four patients with 48 procedures had DSA follow-up at a mean and median time of 7.7 ± 4.5 and 6 months, respectively (range, 3–18 months). The mean degree of stenosis before and after treatment was $69.3 \pm 29.8\%$ and $47.9 \pm 45.1\%$, respectively. Using a paired samples test, the difference of stenosis rates between initial and follow-up DSA evaluation was reduced significantly (21.31 ± 26.88 , 95% confidence interval [CI] 13.58–29.03, $t = 5.55$, $p < 0.001$).

The composite improved lesion rate was 50.0% (24/48) and one new lesion in the right posterior cerebral artery was detected whereas 47.9% (23/48) were observed to have no change in arterial stenosis. Kaplan–Meier survival analysis revealed that the 13-month cumulative improved lesion rate was $40.3 \pm 8.7\%$, and remained the same at 18 months. The mean time to lesion improvement was 12.58 ± 0.96 months (95% CI 10.70–14.46) and the median time was 13 ± 3.88 months (95% CI 5.39–20.61).

4. Discussion

Cerebral vasculitis is difficult to diagnose with confidence, because not all patients display clinical or laboratory signs of inflammation.⁸ Moreover, the so-called classic angiographic findings of arteritis are non-specific. With respect to our patients who showed intracranial arterial stenosis as evidenced by neuroradiological

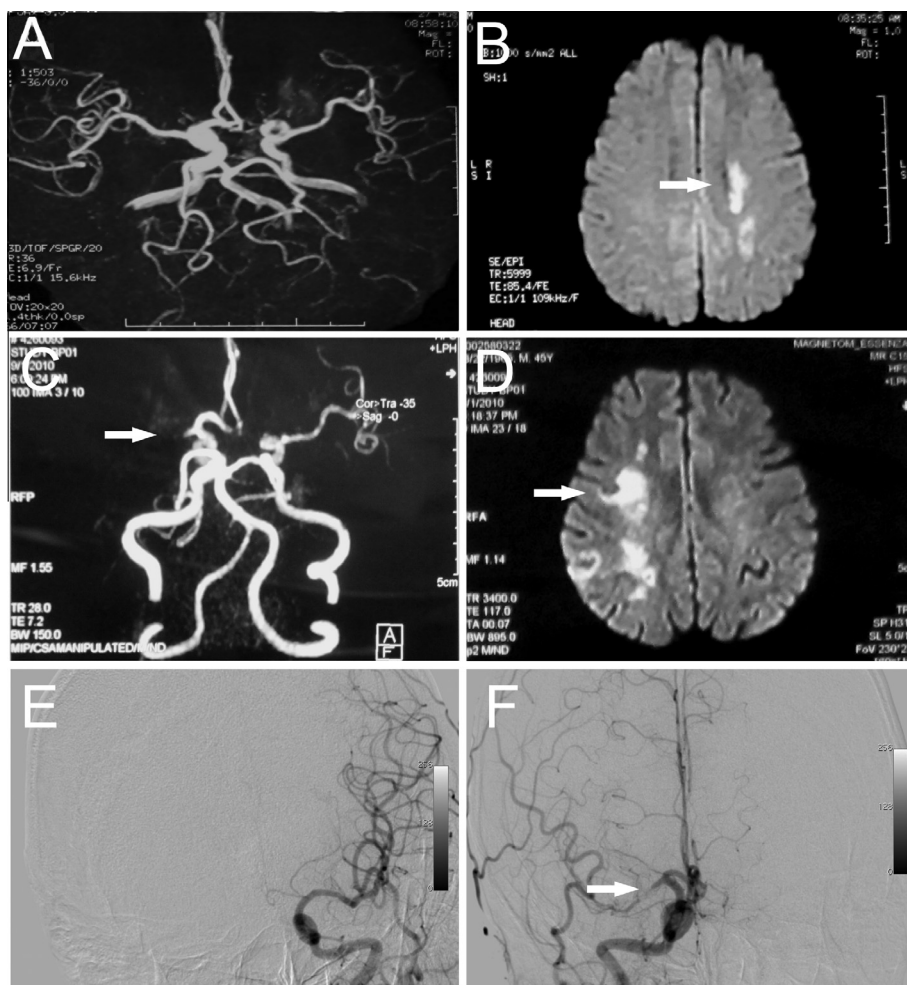


Fig. 2. Patient 23 (A) magnetic resonance angiograms showing no obvious cerebral artery stenosis 1 day after his first stroke, (B) axial diffusion-weighted MRI showing acute infarction in the left cerebral hemisphere at his first stroke, (C) magnetic resonance angiograms showing right middle cerebral artery severe stenosis 9 hours after his second stroke, (D) axial diffusion-weighted MRI showing an acute infarction in the right cerebral hemisphere after his second stroke. Digital subtraction angiograms showing (E) a normal left middle cerebral artery and (F) right middle cerebral artery with a 99% stenosis.

findings (MRI, angiogram), we failed to find any risk factors for atherosclerosis. In addition, all the parameters of the laboratory tests were normal except for the elevated IgE serum levels. Interestingly, corticosteroid (dexamethasone and/or prednisone) treatment did not only alleviate the symptoms but also significantly improved intracranial arterial stenosis. Therefore, all the patients were diagnosed as possibly having cerebral vasculitis based on the clinical, laboratory and therapeutic characteristics.

Our findings undoubtedly suggest a causative role of vasculitis in intracranial arterial stenosis. However, we failed to categorize the subtypes of vasculitis in all patients due to a lack of histopathologic or post mortem examination. In recent years, vasculitis has received much attention because many of these diseases can be organ- or even life-threatening. Unfortunately, the pathogenesis of vasculitis remains elusive.⁹ Immunosuppressive and cytotoxic agents are still the only effective drugs to manage most vasculitic diseases. Abnormalities of immunological parameters can be found in most of these diseases.¹⁰ However, to our knowledge, a single immunological parameter (IgE serum level) abnormality in vasculitis has not been described before. As we know, elevated IgE serum level can also be found in patients with Churg–Strauss Syndrome (CSS).^{11,12} However, we can rule out the diagnosis of CSS based on the lack of other features of CSS in all our patients.

Previous studies have reported that reduced interleukin (IL)-2, but elevated IL-4, IL-6, and IgE can be found in patients with cerebral infarction during the acute stage.⁶ It seems to be a T helper 2 cell response to brain injury. After the cerebral infarction, these cytokines are implicated in a wide range of pathologic processes. In addition, several studies have found a transient rise of serum IgE levels in patients with acute coronary syndromes,¹³ indicating the role of an acute inflammatory response in plaque rupture. These reports suggested that IgE may function as an acute phase protein during acute ischemic diseases. However, another report focused on the predictive role of IgE during acute myocardial infarction, and found IgE may predict future non-fatal myocardial infarction in men and appears to be an independent prospective risk factor for coronary diseases.⁴ We unexpectedly found the serum IgE level in our patients remained at a high level 3 months after the first admission. The unaltered IgE levels suggested that IgE may not be an important factor in the acute stage although we cannot rule out this possibility. Of course, it is unknown if IgE is a harbinger of future cerebral incidents based on our findings. It is urgent to determine if IgE is an ischemic cerebral disease risk factor and whether it is involved in the pathogenesis of vasculitis, or if it is indicative of the participation of immunoglobulin in an inflammatory response to tissue damage.

It is accepted that IgE concentrations are correlated with antigen-activated mast cells which are regarded as an early responder during brain ischemia.⁶ Local antigen stimulation of IgE-bound mast cells may lead to foam cell formation within arterial walls. Of our 26 patients, two were found to be hypersensitive to dust mites. It is reasonable to imagine that some unknown triggers, such as dust mites, elicited type I allergic reactions and so may be involved in the process of arteriostenosis. However, the role of

an IgE-mediated allergic response during vasculitis remains to be further investigated.

In our study, we report 26 patients with possible vasculitis-associated ischemic cerebral disease, which was characterized by a persistent high level of serum IgE. It should be noted that there were no tissue biopsy results provided to confirm the diagnosis of vasculitis. Tissue biopsy results might provide important and direct evidence to reduce the difficulty of diagnosing vasculitis. But in China, tissue biopsy is not commonly performed and there is difficulty in obtaining patient consent to obtain a tissue sample, especially brain tissue. Another limitation of this study was that we couldn't exclude arterial dissection as the cause of cerebral arteriostenosis for some patients, as they were only diagnosed by angiography. Notwithstanding its limitations, this study does suggest that the non-atherosclerotic pathway for arterial stenosis in ischemic cerebral diseases merits attention, particularly in those patients without risk factors of atherosclerosis.

Conflicts of Interest/Disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

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