

Guillain-Barré Syndrome Triggered by Surgery in Chinese population: Towards a Multicenter Retrospective Study

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Abstract

Background

Surgery is described as a potential trigger of Guillain-Barré syndrome (GBS). The present study was designed to explore the clinical feature of post-surgical GBS compared with those of general GBS, to give better clinical advice to patients undergoing surgery.

Methods

We retrospectively analyzed medical records of GBS patients in 31 representative tertiary hospitals, located in 14 provinces in southern China, between 1 January 2013 and 30 September 2016. Post-surgical GBS was defined as symptoms of GBS within 6 weeks after surgery. We described clinical feature of post-surgical GBS, and assessed the difference between post-surgical GBS and the general GBS.

Results

Of the 1001 GBS patients enrolled, 45 patients (4.5%) had undergone surgery within 6 weeks before GBS symptom onset. Among them, 36 patients (80.0%) developed initial symptoms of limb weakness. The average interval between surgery and symptom onset was 13.31 days. The most common type of surgery triggering GBS was orthopedic surgery, followed by neurological surgery. Compared to the general GBS, post-surgical GBS was characterized by higher proportion of severe patients (HFGS ≥ 3) on admission and at nadir, higher HFGS score at discharge, and longer hospital stays. Besides, the post-surgical GBS patients had a significantly higher frequency of the subtype of AMAN (37.9 vs 14.2, $P=0.001$).

Conclusion

Surgery was a potential trigger factor for GBS, especially in orthopedic surgery. The clinical presentation of postsurgical GBS was characterized by a more severe course and poorer prognosis.

Clinical trial registration

chicTR-RRc-17014152.

Background

Guillain-Barré syndrome (GBS) is an immune-mediated acute polyradiculoneuropathy, characterized by rapidly progressive muscular weakness, and hyporeflexia or areflexia^[1]. Antecedent infections 6 weeks prior to symptom onset are presented in about 2/3 of GBS patients^[2]. Besides, non-infectious factors such as vaccinations, trauma and surgery were reported as possible triggers. Several case reports described the occurrence of GBS following cardiac surgery, gastrointestinal surgery, neurological surgery, orthopedic surgery, laparoscopic prostatectomy, and so on^[3-15]. H. Gensicke et al. found that the

incidence of GBS after surgery was significantly higher than that of GBS triggered by infection or vaccine^[16]. Surgery was probably a potential risk factor for the occurrence of GBS^[17]. All 9 patients enrolled in Xiaowen Li, et al's study exhibited an axonal rather than demyelinating form of neuropathy^[18]. Moreover, Sara Hocker et al. reported that post-surgical GBS was more common in patients with an active malignancy^[19]. A previous study including 17 post-surgical GBS patients and 66 non-surgical GBS patients showed that post-surgical GBS patients had severe motor dysfunction and poor prognosis^[20]. However, previous studies were limited in a small sample. The clinical features of post-surgical GBS were not well understood, and it remains unclear whether post-surgical GBS presents with a more severe course or poorer prognosis, compared with the GBS triggered by other risk factors. And what kind of surgery patients should be particularly concerned about?

To date, the above theme has not been explored systematically in a large cohort of GBS patients. Thus, we performed a multicenter retrospective study to explore the clinical feature of post-surgical GBS, as an aid to clinical early warning and early intervention.

Methods

Patients

We retrospectively reviewed the medical records of consecutive hospitalized patients with a diagnosis of GBS in 31 representative tertiary hospitals, located in 14 provinces in southern China, between 1 January 2013 and 30 September 2016^[21]. The diagnosis of each GBS patients were verified, meeting the established clinical criteria of Asbury and Cornblath (1990)^[22]. And details of clinical data extraction and analysis were described specifically in our previous study^[21].

This study was approved by the ethics committee of the Renmin Hospital of Wuhan University, Wuhan, China. The informed consent was waived.

Variables

Clinical data collected included age, sex, antecedent infections, history of diabetes mellitus and hypertension, initial symptoms, Hughes score on admission, time between surgery and symptom onset, type of surgery, cerebrospinal fluid (CSF), Hughes score at nadir, duration of hospitalization, Hughes score at discharge, requirement for mechanical ventilation, modality, electrodiagnostic subtypes and treatment. Electrodiagnostic criteria proposed by Hughes^[23] (online supplementary table) was used to define GBS subtypes in patients with available electrophysiologic data. Post-surgical GBS was defined as symptoms of GBS within 6 weeks after surgery.

We described clinical features of postsurgical GBS, and compared the differences between GBS after surgery and GBS without recent surgery.

Evaluation of disease severity and short-term prognosis

Hughes Functional Grading Scale (HFGS) score^[24], a widely accepted scale of disability for GBS (Grade 0, healthy; grade 1, minor signs or symptoms of neuropathy but capable of manual work; grade 2, able to walk without support of a stick but incapable of manual work; grade 3, able to walk with a stick, appliance, or support; grade 4, confined to bed or chair bound; grade 5, requiring assisted ventilation; grade 6, dead) was applied. A severe form of the disease was defined as Hughes score above or equal 3 on admission or at nadir, and good short-term prognosis defined as Hughes score below 3 at discharge.

Statistical analysis

Statistical analysis was performed with SPSS V.25.0 software (IBM, West Grove, Pennsylvania, USA). Categorical data were reported using proportions, while continuous data with means and standard deviations. The chi-square and Fisher exact tests were used to find out whether differences in proportions are significant. Student's t-test was performed to analyze continuous variables normally distributed, and Mann-Whitney U test or the Wilcoxon Signed Rank Test was used to compare non-normally distributed data. $P < 0.05$ was considered to be significant.

Results

In total, 1001 GBS patients were enrolled, men (60.0%) and women (40.0%), with a mean age of 51.48 years. Among them, 45 patients (4.5%) had undergone surgery within 6 weeks before symptom onset, accordingly identified as post-surgical GBS.

Characteristics of post-surgical GBS patients

The demographic characteristics and clinical features of post-surgical GBS were presented in Table 1. The group consisted of 19 women (42.2%) and 26 men (57.8%), with a mean age of 53.93 years (SD 12.86, range 24–79). The average interval between surgery and symptom onset was 13.31 days, ranging from 1 to 40 days. And symptoms of GBS appeared within 2 weeks after surgery in 67% of patients (Fig. 1). Among them, 36 patients (80.0%) developed initial symptoms of motor weakness, while 12 patients (25.2%) developed initial symptoms of sensory change. 11 patients (24.4%) had a history of hypertension, and 4 patients (8.9%) with a history of Diabetes mellitus. Lumbar puncture was carried out in 31 patients, among whom 23 patients presented albumino-cytological dissociation. Electromyographic data of 29 patients were available. According to the electrophysiological criteria, 12 of 29 patients were diagnosed with acute inflammatory demyelinating polyneuropathy (AIDP); 11 with acute motor axonal neuropathy (AMAN); 2 with acute motor sensory axonal neuropathy (AMSAN); 1 with normal; and 3 with equivocal results. HFGS score were applied to assess clinical severity and prognosis. The proportion of severe patients (HFGS ≥ 3) on admission, or at nadir was 82.2% and 91.1%, respectively, and the average of HFGS score at discharge was 2.78 (Table 1). All patients were treated actively after admission, among whom 18 patients were treated with intravenous immunoglobulin; 10 with glucocorticoid; 15 with combination of intravenous immunoglobulin and glucocorticoid; 1 with plasmapheresis; and 1 with combination of glucocorticoid and plasmapheresis.

Table 1

The demographic characteristics and clinical features of post-surgical GBS and general GBS.

Parameters	GBS without recent surgery (n = 956)	GBS after surgery (n = 45)	Two-tailed P value
Age (mean, years)	51.37 ± 15.85	53.93 ± 12.86	0.285
Male, n (%)	575(60.1%)	26(57.8%)	0.751
Diabetes mellitus, n (%)	72(7.5%)	4(8.9%)	0.962
Hypertension, n (%)	241(25.2%)	11(24.4%)	0.908
Initial symptoms, n (%)			
Motor weakness	729(76.3%)	36(80.0%)	0.563
Sensory change	402(42.1%)	12(25.2%)	0.041
Hughes score on admission, n (%)			
≥ 3	608(63.6%)	37(82.2%)	0.011
< 3	348(36.4%)	8(17.8%)	
Hughes score at nadir, n (%)			
≥ 3	692(72.4%)	41(91.1%)	0.006
< 3	264(27.6%)	4(8.9%)	
Hospital stay (mean, days)	17.18 ± 11.22	24.58 ± 19.75	0.000
Hughes score at discharge (mean, g)	2.09 ± 1.26	2.78 ± 1.35	0.001
Mechanical ventilation (MV), n (%)	91(9.5%)	4(8.9%)	1.000
Death in hospital stay, n (%)	6(0.6%)	1(2.2%)	0.276
Lumbar puncture	757	31	
Mean protein concentration (g/L)	1.18 ± 0.86	0.99 ± 0.71	0.346
Albumin-cytologic dissociations, n (%)	611(80.7%)	23(74.2%)	0.370
Electrodiagnostic subtypes, n (%)	691	29	
AIDP	339(49.1%)	12(41.4%)	0.418
AMAN	98(14.2%)	11(37.9%)	0.001

AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; AMSAN, acute motor sensory axonal neuropathy; GBS, Guillain-Barré syndrome; IVIg, intravenous Immunoglobulin; Statistically significant results are in bold.

Parameters	GBS without recent surgery (n = 956)	GBS after surgery (n = 45)	Two-tailed P value
AMSAN	21	2	0.236
Treatment, n (%)			
IVIg	407(42.6%)	18(40.0%)	0.733
Plasmapheresis	41(4.3%)	1(2.2%)	0.768
AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; AMSAN, acute motor sensory axonal neuropathy; GBS, Guillain-Barré syndrome; IVIg, intravenous Immunoglobulin; Statistically significant results are in bold.			

Categories of surgeries

The details of surgeries were shown in Table 2. The most common type of surgery triggering GBS was orthopedic surgery, with a proportion of 46.7%; followed by neurological surgery (17.8%); followed by ophthalmic surgery and gastrointestinal surgery (8.9%); followed by cesarean delivery (6.7%); followed by coronary bypass surgery (4.4%); then followed by artificial abortion, thoracic surgery and vocal cord polyp resection (2.2%).

Table 2
Categories of surgeries.

Type of surgery	N (%) (total n = 45)
Orthopedic surgery	21(46.7%)
Fracture	9
Lumbar intervertebral disc	6
Lumbar stenosis	1
Lumbar spondylolisthesis	1
Cervical internal disc herniation	1
Hemangioma of the phalanx	1
Foot injury	1
Bone graft	1
Neurological surgery	8(17.8%)
Subdural hematoma	2
Hydrocephalus	2
Meningioma	1
Hypophysoma	1
Cerebral aneurysm	1
Trifacial neuralgia	1
Ophthalmic surgery	4(8.9%)
Glaucoma	1
Retinal detachment	1
Conjunctival melanoma	1
Ocular trauma	1
Gastrointestinal surgery	4(8.9%)
Gastric polyps	1
Esophageal carcinoma	1
Appendicitis	1
Cholecystitis	1
Cesarean delivery	3(6.7%)

Type of surgery	N (%) (total n = 45)
Artificial abortion	1(2.2%)
Coronary bypass surgery	2(4.4%)
Thoracic surgery	1(2.2%)
Vocal cord polyp resection	1(2.2%)

Comparison of disease severity and prognosis between GBS patients without recent surgery and GBS after surgery

The details were shown in Table 1. Compared with GBS patients without recent surgery, GBS after surgery were characterized by higher proportion of severe patients (HFGS ≥ 3) on admission (82.2 vs 63.6, $P = 0.011$) and at nadir (91.1 vs 72.4, $P = 0.006$), higher HFGS score at discharge (2.78 ± 1.35 vs 2.09 ± 1.26 , $P = 0.001$), and longer hospital stays (24.58 ± 19.75 vs 17.18 ± 11.22 , $P = 0.000$). Besides, the post-surgical GBS patients had a significantly higher frequency of the subtype of AMAN (37.9 vs 14.2, $P = 0.001$), while a significantly lower frequency of developing initial symptoms of sensory change (25.2 vs 42.1, $P = 0.041$). No significant difference was found in other variables.

Discussion

In this multicenter retrospective study including 1001 GBS patients, surgery was a potential trigger factor for GBS that should not be ignored, especially in orthopedic surgery. Furthermore, post-surgical GBS presented with a more severe course and poorer prognosis, compared with the GBS triggered by other risk factors.

Previous studies reported an occurrence of post-surgical GBS of 9.1%^[19], 6.6%^[25], 19.4%^[26], 5.8%^[27] and 9.5%^[16], respectively. In the present study, 45 of 1001 (4.5%) patients were determined as post-surgical GBS, lower than what was reported in the studies above. Such bias could be explained by small sample size of previous studies. Post-surgical GBS showed a male preponderance, with a gender ratio of 3.5 between male and female patients^[26]. However, no gender differences were found in the present study, when compared with the general GBS patients. When it came to the effect of age on morbidity, disagreement arose, comparing post-surgical GBS with general GBS. A literature review revealed that there was a peak in occurrence of post-surgical GBS between ages 50 and 70 years^[17]; while Sejvar et al. indicated that there were two peaks in the general GBS, the first in the young adult population (age 20–30 years) and another in the elderly population (age > 60 years)^[28]. The mean age of post-surgical GBS patients was 53.93 years. No age differences were found in the present study, when compared with the general GBS patients.

Surgical operations caused immunosuppression in the post-operative period, the degree or duration of which was determined by the magnitude of the initial surgical insult^[29]. The immunosuppressive effect

was strongest on the third day after the operation, and it recovered on 7–10 days^[17]. It might help explain why results show that symptoms of GBS appeared within 2 weeks after surgery in 67% of patients. And 36 of 45 (80.0%) post-surgical GBS patients presented limb weakness initially. Therefore, patients with symmetrical limb weakness symptoms within two weeks after surgery should be especially vigilant for GBS.

Orthopedic surgery was the most common surgery type triggering GBS, followed by neurological surgery, which were prone to causing neurologic complications, including spinal cord ischemia, spinal cord hemorrhage, cauda equina syndrome, direct injury to nerves, epidural abscess^[17] and so on, as important differential diagnosis for GBS. Clinical manifestation and required physical examination or image could determine the diagnosis.

The underlying pathogenesis of postsurgical GBS is not fully understood. Several mechanisms were thought to be involved. First, sensitizing mechanism might play a role, in which surgery promoted antigens release and subsequent antigen autoimmunity, contributing to the development of GBS^[30]. Then, surgical operations caused immunosuppression in the post-operative period, which made it failed to prevent the auto-antibodies from attacking the peripheral nerves. Furthermore, post-surgical patients had elevated risk of infections due to immunosuppression. A previous study showed that 42.8% of postsurgical GBS patients encountered infections^[26]. Besides, the endocrine stress systems were activated resulting from surgical operations, followed by hypersecretion of adrenocorticotrophic hormone, which caused the imbalance of immune system^[17,31–33]. Surgical trauma/traction, tourniquet pressure, and malposition of the patient with resultant pressure on a nerve also increased susceptibility to nerve damage. During surgery, various instruments and devices, such as retractors, can compress nerves directly^[34], more common in orthopedic surgery, which could explain why orthopedic surgery are more prone to triggering GBS.

AIDP and AMAN were two important subtypes of GBS. A previous study showed that 15 of the 17 postsurgical GBS patients were diagnosed with AMAN and the other 2 with AMSAN^[20]. In the present study, compared with GBS patients without recent surgery, the post-surgical GBS patients had a significantly higher frequency of the subtype of AMAN, while a significantly lower frequency of developing initial symptoms of sensory change. It indicated that post-surgical GBS patients were more likely to have axonal damage. However, as a retrospective study, we got insufficient information on electrophysiological data of post-surgical GBS patients. More studies are needed to reveal the electrophysiological features of post-surgical patients. Besides, patients with AMAN frequently had serum antibodies against GM1a, GM1b, GD1a and GalNAc-GD1a gangliosides^[1, 2]. Such antibodies that targeted ganglioside complexes promoted complement activation, followed by peripheral nerve injury^[2]. More studies are needed to confirm the distribution of anti-ganglioside antibodies in post-surgical patients.

A previous study showed that post-surgical GBS patients manifested severe motor dysfunction, high risk of respiratory failure, and poor prognosis^[20]. In line with that, our results revealed that higher HFGS

scores, no matter on admission, at nadir or at discharge, were found in post-surgical GBS patients, indicating remarkable increases in disease severity and adverse short-term outcomes. It could be explained as follows: patients with an axonal form presented severer clinical courses and poor prognosis, compared to patients with a demyelinating form; stress and traumas induced by operations themselves were additional blows to the recovery of disease. Besides, we found no significant between-group differences in terms of mechanical ventilation and death in hospital stay.

The present study had limitations. First, it was a retrospective study. The total number of surgical cases during the time was not available, which could serve as the denominator for the incidence of postsurgical GBS. Further work is needed. Then, information on long-term follow-up of postsurgical GBS patients was lacking. However, the large sample size of multi-center study guaranteed the reliability of our research.

Conclusion

The present study supported surgery as a potential trigger factor for GBS, especially in orthopedic surgery. The clinical presentation of post-surgical GBS was characterized by a more severe course and poorer short-term prognosis. Such patients mainly developed weakness symptoms initially within two weeks after surgery. Therefore, when postoperative patients appear unexplained progressive muscle weakness, GBS should be noted and appropriate treatment should be taken to alleviate symptoms. If necessary, physicians should transfer them to the intensive care unit in time. Early diagnosis may help to initiate appropriate treatment soon, thus improving prognosis.

Abbreviations

GBS, Guillain-Barré syndrome; HFGS, Hughes Functional Grading Scale; CSF, cerebrospinal fluid; AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; AMSAN, acute motor sensory axonal neuropathy; SD, Standard Deviation.

Declarations

Ethics approval and consent to participate

This retrospective study was approved by the ethics committee of the Remin hospital of Wuhan University, Wuhan, china. The informed consent was waived.

Consent for publication

Not applicable.

Availability of data and materials

Data used for analysis are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

QG contributed to the study design. QG, SL, YL, JY and XF contributed to data collection and analysis. QG wrote the manuscript. ZL and ZX reviewed the manuscript. All authors read and approved the final manuscript.

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Figures

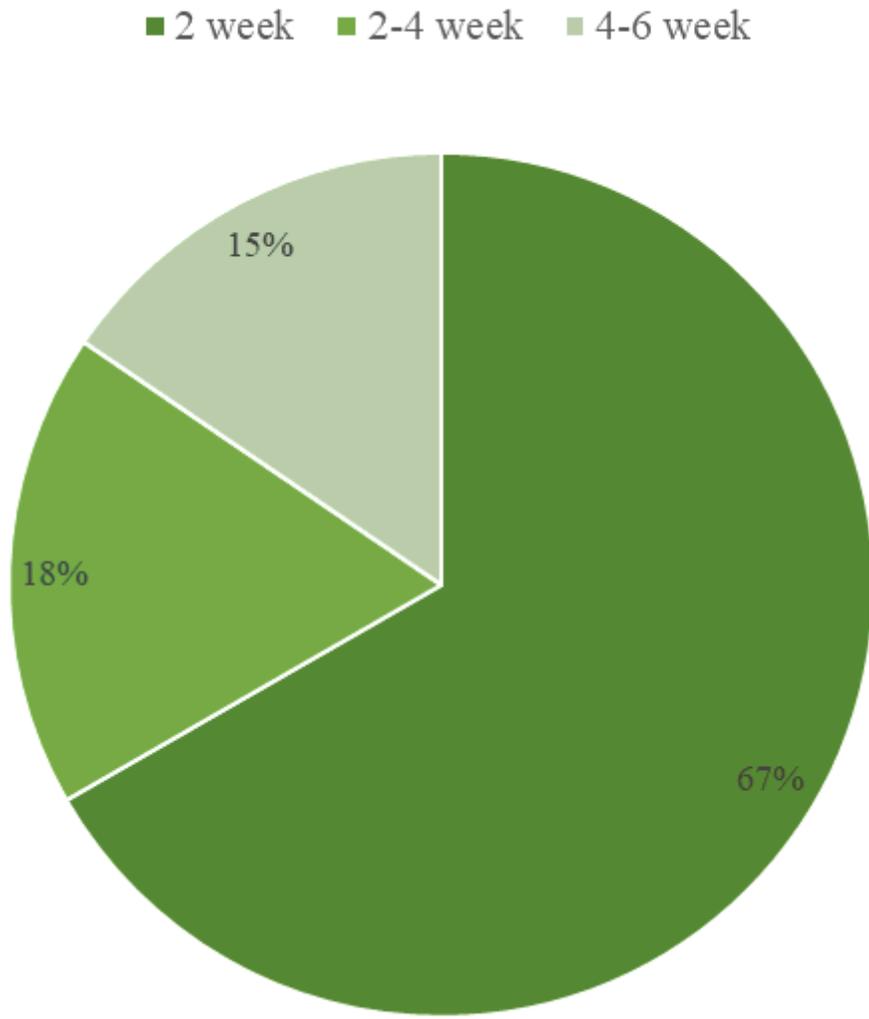


Figure 1

The bar graph showing distribution of interval between surgery and GBS.

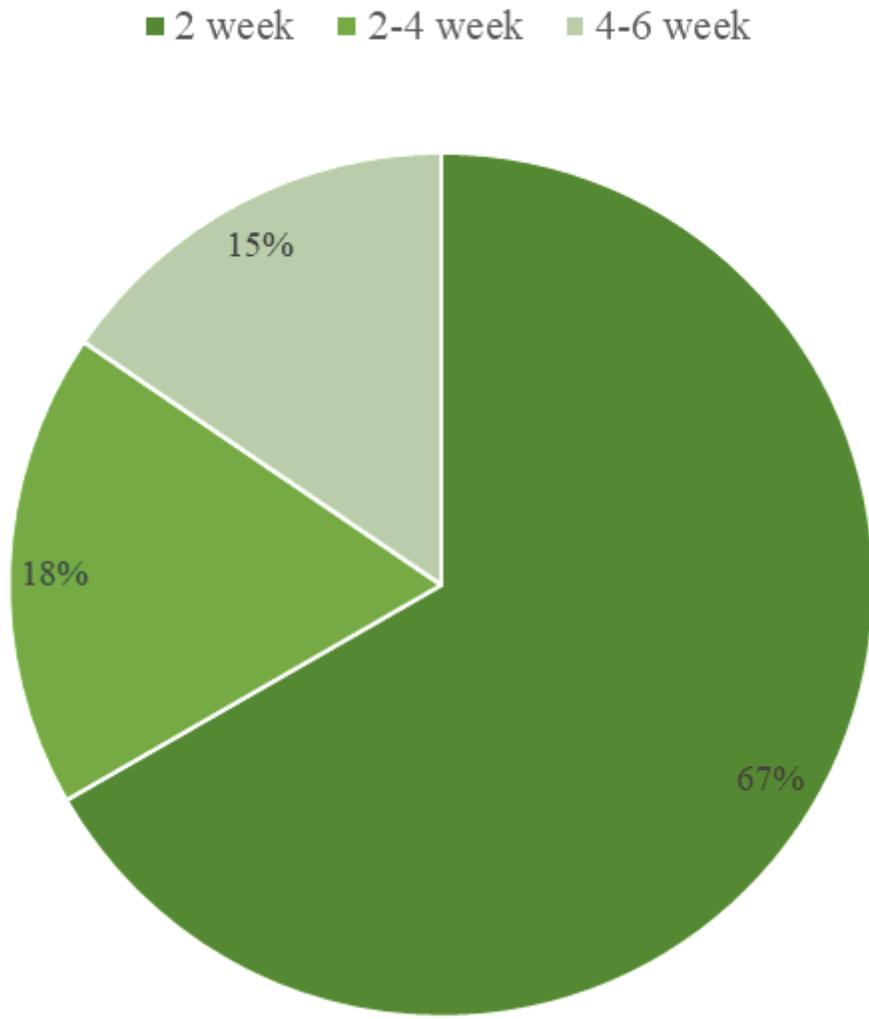


Figure 1

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