Saethre–Chotzen syndrome: long-term outcome of a syndrome-specific management protocol

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ABBREVIATIONS

FOA	Fronto-orbital advancement
ICH	Intracranial hypertension
OCT	Optical coherence tomography
OFC	Occipital frontal head circumference
OSA	Obstructive sleep apnoea

AIM To assess the long-term outcomes of our management protocol for Saethre–Chotzen syndrome, which includes one-stage fronto-orbital advancement.
METHOD All patients born with Saethre–Chotzen syndrome between January 1992 and March 2017 were included. Evaluated parameters included occipital frontal head circumference (OFC), fundoscopy, neuroimaging (ventricular size, tonsillar position, and the presence of collaterals/an abnormal transverse sinus), polysomnography, and ophthalmological outcomes. The relationship between papilledema and its associated risk factors was evaluated with Fisher's exact test.
RESULTS Thirty-two patients (21 females, 11 males) were included. Median (SD) age at first surgery was 9.6 months (3.1mo) for patients who were primarily referred to our center (range: 3.6–13.0mo), the median (SD) age at last follow-up was 13 years (5y 7mo; range: 3–25y). Seven patients had papilledema preoperatively, which recurred in two. Two patients had papilledema solely after first surgery. Second cranial vault expansion was indicated in 20%. Thirteen patients had an OFC deflection, indicating restricted skull growth, one patient had ventriculomegaly, and none developed hydrocephalus. Eleven patients had emissary veins, while the transverse sinus was aberrant unilaterally in 13 (hypoplastic n=10 and absent n=3). Four patients had mild tonsillar descent, one of which was a Chiari type I malformation. Four patients had obstructive sleep apnoea (two mild, one moderate, and one severe). An aberrant transverse sinus was associated with papilledema (p=0.01).
INTERPRETATION Single one-stage fronto-orbital advancement was sufficient to prevent intracranial hypertension for 80% of our patients with Saethre–Chotzen syndrome. Follow-up should focus on OFC deflection and venous anomalies.

Saethre–Chotzen syndrome is a craniosynostosis syndrome, which arises in 1 per 100 000 live births.[1] Its clinical features include uni- or bicoronal synostosis, low hairline, external ear abnormalities, ptosis of the upper eyelid(s), tear duct stenosis, hypertelorism and anomalies of the hand (such as syndactyly and brachydactyly), and short stature.[2,3] Clinical diagnosis in these patients is genetically confirmed by a deletion or mutation in the *TWIST1* gene.[4–6]

The management of patients with Saethre–Chotzen syndrome consists of a multidisciplinary approach, and focuses on several aspects regarding child development such as hearing capacity; speech, language, and neuropsychological development; vision; dental outcomes; and management of the airway. Additionally, prevention of intracranial hypertension (ICH) is a major goal. Literature on the presence, causes, and treatment of ICH in patients with Saethre–Chotzen syndrome is limited. The reported prevalence of ICH before surgery, defined by papilledema on fundoscopy or by ICH on intraparenchymal measurement, varies between 19% and 35%.[2,7] Occurrence of ICH after vault expansion is reported in 17% to 42% of patients,[3,7] which is remarkably lower than reported for patients with Apert and Crouzon syndromes.[7,8] Our preferred surgical treatment for Saethre–Chotzen syndrome is a single fronto-orbital advancement (FOA) for three reasons: (1) second cranial vault expansion is seldom indicated, (2) there is no

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anticipated need for mid-face advancement in the future, which is more complicated after an FOA, and (3) FOA restores the distorted facial profile.

The aim of this study was to evaluate the long-term outcome of our management protocol for patients with Saethre–Chotzen syndrome by determining the prevalence of ICH and its risk factors.

What this paper adds

- A single cranial vault expansion can prevent intracranial hypertension (ICH) in patients with Saethre–Chotzen syndrome.
- Only 20% of patients need a second craniofacial procedure.
- The main contributors to ICH are venous anomalies and occipital frontal head circumference deflection.

METHOD

Participants

All patients with Saethre–Chotzen syndrome born between 1992 and 2017, who were treated at the Dutch Craniofacial Center (Erasmus University MC – Sophia Children's Hospital, Rotterdam, the Netherlands), were included in this study. Children born after 2005 were prospectively included and children born before 2005 were retrospectively included. Patients with unavailable data for more than three variables (see below) were excluded. The study was approved by the ethics committee of Erasmus MC (MEC-2005-273 and MEC-2016-312). All patients were genetically tested, and since the phenotype was clear in the majority of patients, genetic testing included targeted sequencing of the *TWIST1* gene, and additional fluorescence in situ hybridization or multiplex ligation-dependent probe amplification in patients with a suspected deletion in, or of, the *TWIST1* gene. In some patients, the *FGFR3* gene (P250R mutation) was also tested.

According to our protocol, routine FOA was performed at the age of 6 to 9 months, with remodelling and advancement of the forehead and supra-orbital bar.[9,10] The orbital rim was advanced approximately 1.5cm, thereby taking into consideration that the facial profile should not be significantly disturbed.

ICH

Patients were screened for the presence of ICH according to our standardized management protocol,[10] which includes assessment of: bulging of the fontanel in calm infants; monitoring of symptoms suggestive of ICH, such as morning headaches and behavioural changes; skull growth: occipital frontal head circumference (OFC) was measured preoperatively, every 3 months until the age of 2 years, every 6 months until the age of 4 years, and from then on annually, and was used as an indicator for intracranial volume;[11] growth curve deflection, defined preoperatively as at least a 0.5 SD fall from baseline and the postoperative baseline established 1 year after surgery defined as at least a 0.5 SD fall from the renewed baseline; fundoscopy: to screen for papilledema, performed once preoperatively, at the ages of 2, 4, and 6 years, and additionally as indicated (pseudopapilledema caused by high hypermetropia was excluded);[12] and optical coherence tomography (OCT) in children aged at least 4 years, using a Spectralis OCT scanner (Heidelberg Engineering, Heidelberg, Germany). The latter was added to the protocol in 2014. The total retinal thickness was analysed using our normative references, which were derived from OCT data of 67 typically developing children (aged 4–12y). Abnormal values included total retinal thickness of less than 276μm or greater than 503μm (unpublished material, van de Beeten et al.), indicating either atrophy or papilledema.

Invasive intracranial pressure monitoring was performed when ICH was suspected, despite the absence of papilledema on repeated fundoscopy with a 6-week interval. This 24-hour examination was evaluated according to the following criteria.[13] (1) Baseline intracranial pressure during the day and overnight: less than 10mmHg, normal; 10mmHg to 15mmHg, borderline abnormal depending on the height and duration of abnormal plateaus; and greater than 15mmHg, abnormal. Additionally, the trend of intracranial pressure values was evaluated to check for any increase overnight. (2) Number of abnormal plateau waves: based on height (<25mmHg, normal; 25–35mmHg, borderline; and >35mmHg, abnormal) and duration (<10mins, normal; 10–20mins, borderline; and >20mins, abnormal).

Patients with papilledema and/or abnormal intracranial pressure measurements were all considered to have ICH.

Neuroimaging

The presence of tonsillar herniation, venous collaterals, and transverse sinuses was reviewed on magnetic resonance imaging (MRI) scans, while ventricular size was evaluated on MRI and computed tomography (CT) scans. A three-dimensional reformatting platform (AquariusNET; TeraRecon Inc., Melbourne, Victoria, Australia) was used to align scans in all planes. CT and MRI studies were part of the standard care protocol.

The presence and extent of tonsillar herniation was evaluated on mid-sagittal and adjacent slices and was classified as: (1) no tonsillar descent, (2) tonsillar descent less than 5mm, or (3) herniation greater than 5mm (i.e. Chiari type I malformation). The position of the lowest tonsil relative to the foramen magnum was measured.

Occipital emissary veins were scored on CT angiography/MRI scans and were classified as either absent or present. The transverse sinuses were scored as normal, hypoplastic, or absent.

The frontal occipital horn ratio was measured on axial planes to evaluate the sizes of the lateral ventricles. A frontal occipital horn ratio greater than 0.34 indicated enlarged ventricles.[14] Hydrocephalus was defined as progressive enlargement of the ventricles on two or more MRI or CT scans.

Sleep studies

Clinical and ambulant sleep studies were used to diagnose obstructive sleep apnoea (OSA). All sleep studies were scored according to the 2012 update of the American

Association of Sleep Medicine.[15] The obstructive apnoea–hypopnea index was calculated by adding the number of obstructive apnoeas, mixed apnoeas, and obstructive hypopneas with desaturation/arousal, divided by the total sleep time. Arousals could only be scored on clinical sleep studies. Patients were subdivided in either mild (obstructive apnoea–hypopnoea index ≥1 and <5), moderate (obstructive apnoea–hypopnoea index ≥5 and <10), or severe (obstructive apnoea–hypopnoea index ≥10) OSA groups.

Analysis of proportional differences

To evaluate proportional differences between patients who underwent one versus two or more cranial vault expansions, one-tailed Fisher's exact tests were used, given that the direction of the effect was anticipated. Likewise, the differences between patients with or without papilledema were evaluated. Variables analysed included OFC growth curve deflection, the presence of venous collaterals, and the aspect of the transverse sinuses (see 'Neuroimaging'). SPSS statistics version 25 (IBM Corp., Armonk, NY, USA) was used to perform the analyses, and statistical significance was set at a $p<0.05$.

Ophthalmological evaluation

Visual acuity testing was routinely performed by an orthoptist, and was assessed by using either a Snellen/Tumbling E-chart or the Amsterdam Picture Chart. Children who were too young to be evaluated for visual acuity completed the fix-and-follow test. The latest available test results were evaluated, since papilledema may have a long-term effect on vision.[13] Confounding caused by strabismus and/or amblyopia was minimalized by using the eye with the best visual acuity. Results were expressed using the logMAR scale.

Cycloplegic refraction was measured and classified according to the classification criteria described by Morgan et al.:[16] highly myopic: up to –6.00D; myopic: up to –0.50D to greater than –6.00D; emmetropic: greater than –0.50D to up to 0.50D; mildly hyperopic: greater than 0.50D to up to 2.00D; hyperopic: greater than 2.00D to up to 6.00D; and highly hyperopic: greater than 6.00D. Refraction was analysed at two time points: in children aged up to 6 years old, when patients are at risk of developing ICH[17] (at this age, refraction data were used to interpret fundoscopy results, since hyperopia at least 3.00D can mimic papilledema on fundoscopy[12]), and at the age of at least 8 years old, since visual development continues up until 7 to 8 years of age.[18]

Neuropsychological functioning

Educational levels were monitored at follow-up visits to the outpatient clinic and used as a proxy for neuropsychological development.

Speech and language development

Speech and language development was routinely monitored, and patients were referred for speech therapy if indicated.

Approval and consent

This study was approved by the ethics committee of the Erasmus MC (MEC-2005-273 and 2017-1143). Patient consent was not required for this study.

RESULTS

Patient characteristics

We included 32 patients (21 females, 11 males). The median (SD) age at first surgery was 10.1 months (33.4mo) for the whole group (range 3.6mo–14y 3mo), while it was 9.6 months (3.1mo) for patients primarily referred to our centre (range 3.6–13.0mo). See Table S1 (online supporting information) for details. The median (SD) age at last follow-up was 13 years (5y 6mo; range: 3–25y). Sixteen patients had bicoronal synostosis, 10 had unicoronal synostosis, and more than two sutures were closed in six patients (Table S1). Five patients were excluded because of unavailable data.

The diagnosis was genetically confirmed in all patients (Table S1). A *TWIST1* gene mutation was identified in 21 patients (substitution n=16, duplication n=4, and insertion n=1), and a deletion in or of the *TWIST1* gene was identified in 11 patients. Two of the substitutions were familial unclassified variants, and family members of these patients had a Saethre–Chotzen-like phenotype. Both patients were tested for the *P250R* mutation in the *FGFR3* gene but it was not found.

Thirty patients were treated according to our management protocol. Twenty-four patients underwent cranial vault surgery once, while second vault expansion was indicated in six. Two patients underwent a third cranial vault expansion in our centre after referral from elsewhere.

ICH

Bulging of the fontanel

There were no infants with bulging of the fontanel.

Symptoms

Thirteen patients had a headache episode, which for two patients was related to ICH because of late referral (patient numbers 22 and 25, Table S1). In the other 11 patients, additional examinations such as fundoscopy, OCT scans, polysomnography, and CT/MRI did not show abnormalities, and the headaches resolved with expectant care. Behavioural changes were not reported.

Skull growth

Nineteen patients had an OFC growth curve deflection once or more during their lifetime, seven of whom had papilledema in their medical histories (see Fig. S1, online supporting information, for OFC growth curve trajectories in patients with vs without papilledema). Five patients showed an OFC growth curve deflection solely before first surgery, whereas a deflection occurred in 12 out of 32 patients after first surgery, and in six out of the eight patients after second skull surgery. The mean OFC in SD before first surgery was –1.59 (range: –5.05 to 0.33).

Fundoscopy

Seven patients had bilateral papilledema preoperatively, which recurred in two patients during follow-up after first surgery. Two patients solely had papilledema during follow-up after first surgery. Two patients had recurring papilledema after two routine cranial vault expansions elsewhere (first surgery FOA and second surgery occipital expansion) (see also Table S1 for detailed information on these patients: numbers 29 and 30).

OCT

Nine patients underwent OCT, two of whom had increased total retinal thickness at the ages of 5 and 8 years. In both patients, papilledema was also noted with fundoscopy. Total retinal thickness was normal in the other seven patients (i.e. no atrophy/papilledema).

Neuroimaging

The lateral ventricles were evaluated on 56 scans (MRI n=28 and CT n=28) from 30 patients. One patient had ventriculomegaly and none developed hydrocephalus.

Eleven out of 24 scored patients had occipital emissary veins. The transverse sinuses were normal in 11 patients, while they were unilaterally hypoplastic in 10 and unilaterally absent in three.

Cerebellar tonsil position was measured on 34 scans in 25 patients (mean age: 6y 6mo and range: 1d–24y 2mo). Four patients had mild tonsillar descent (16%), while one had a Chiari type I malformation (4%).

The seven patients who did not undergo MRI either had dental braces (n=3) or the parents/patient did not consent to MRI (n=4). See Table S1 for outcomes of neuroimaging.

OSA

Twenty-two patients underwent a polysomnography, four of whom had OSA (two mild, one moderate, and one severe) (Table S1). Polysomnography was performed routinely in the two patients with mild OSA, whereas OSA was indicated in the other two patients because of snoring/sleep problems. One of the latter two patients was measured clinically, while the other one was ambulant because of the parents' preference. Cheyne Stokes breathing patterns were not detected in our cohort.

Coherence of risk factors for and symptoms of ICH

Patients with cranial vault surgery: single cranial vault expansion versus expansion at least twice

Eight patients required a second cranial vault expansion. Six were treated according to our management protocol. Cranial vault surgery was indicated by papilledema in one patient, whereas two patients had severe impressions on X-ray imaging of the skull, indicating craniocerebral disproportion. Three patients had both papilledema and impressions/obliterated subarachnoid space on the CT scan (i.e. signs of craniocerebral disproportion). Preoperatively, OFC deflection was present in five patients and one patient had moderate OSA due to choanal atresia. Emissary veins were seen in three patients, while the transverse sinus was aberrant in four (two patients did not undergo CT angiography/MRI before second vault expansion). Two patients underwent a routine two-stage procedure elsewhere: FOA first, followed by occipital expansion. They both had papilledema at the primary visit to our centre, for which we performed a third cranial vault expansion (occipital expansion). Before surgery, one of them had a deflecting OFC growth curve while the other had no risk factors for ICH (i.e. OSA, OFC deflection, or hydrocephalus). Collaterals were seen in one, while both had an abnormal transverse sinus.

For an overview of proportions in patients who underwent surgery twice or more versus one, see Table 1.

Patients with papilledema versus no papilledema

Of all nine patients with papilledema who were treated according to our protocol, five had an OFC deflection before they showed papilledema on fundoscopy. Occipital collaterals were present in five out of eight patients assessed (one did not undergo CT angiography/MRI before/during the papilledema episode), while the transverse sinus was aberrant in seven out of eight patients. Transverse sinus anomalies were significantly more prevalent in patients with versus without papilledema (p=0.01, Table 2).

Patients with tonsillar descent/Chiari type I malformation

Four out of the five patients with mild tonsillar descent never had papilledema. Three patients had an OFC growth curve deflection before first surgery (patient numbers 14, 16, and 32; Table S1). One had an OFC deflection before first and second surgery (patient number 31; Table S1),

Table 1: Factors influencing proportional differences between the number of cranial vault expansions

	Patients undergoing 1 cranial vault expansion (n)	Patients undergoing ≥2 cranial vault expansions (n)	p[a]
OFC growth curve deflection[b]			
Yes	7	5	0.03
No	17	1[c]	
Venous hypertension			
Emissary veins			
Yes	6	3	0.17
No	12	1	
Transverse sinus hypoplastic/aplastic			
Yes	7	4	0.045
No	11	0	

The two patients who were not primarily referred to our centre were left out of the analysis. [a]Fisher's exact test, one-tailed p-values (left side). [b]OFC deflection was scored 'ever' after first surgery in patients who underwent cranial vault expansion once, and before second cranial vault expansion in patients who underwent cranial vault expansion at least two times. [c]Impressions on X-ray skull and computed topography images at the age of 2 years 1 month. OFC, occipital frontal head circumference.

Table 2: Factors influencing proportional differences between patients with and without papilledema

	Patients with papilledema	Patients without papilledema	p^a
OFC growth curve deflection[b]			
Yes	5	11	0.60
No	4	10	
Venous hypertension			
Emissary veins			
Yes	5	4	0.13
No	3	10	
Transverse sinus hypoplastic/aplastic			
Yes	7	4	0.01
No	1	10	

The two patients who were not primarily referred to our centre were left out of this analysis. [a]Fisher's exact test, one sided *p*-value (right side). [b]The existence of OFC deflection was scored as either before the development of papilledema or 'ever' in patients who never developed papilledema. OFC, occipital frontal head circumference.

and at that time papilledema was also noted on fundoscopy. One patient with mild tonsillar descent underwent MRI repeatedly (patient number 14; Table S1). Mild tonsillar descent was diagnosed at the age of 15 years 8 months, while it was absent on three previous MRI scans between the ages of 7 years 10 months and 10 years 4 months.

Ophthalmological evaluation

Visual acuity was evaluated in 22 patients, with the mean age at evaluation 9 years 7 months (range: 3y 6mo–24y 10mo; see Table S1). Ptosis of the upper eyelid was established in 14 patients, which was bilateral in five cases.

Sixteen patients had their cycloplegic refraction analysed at the age of at least 8 years. One patient had emmetropia and one was diagnosed with myopia. Six patients had mild hyperopia, seven patients had hyperopia, and one patient had high hyperopia.

Neuropsychological functioning

Twenty-four children went to a normal school. Three children followed an individualized curriculum at a specialist school, all because of intellectual disability (mild in one). Three patients were in nursery school. Information regarding educational level was missing for two patients.

Speech and language development

Twelve patients were referred to a speech therapist because of a speech and language delay, seven of whom had hearing loss. Two patients had intellectual disability, which was presumably related to the whole-gene deletion. Two other patients were assumed to have a delay because they were bilingual, and one had an overall motor development delay causing speech problems. Data regarding referral were lacking for seven patients and consecutive speech reports were not available for the whole cohort.

DISCUSSION

In this study, we evaluated the outcomes of our standard management protocol for patients with Saethre–Chotzen syndrome: a single FOA. A second cranial vault expansion because of ICH was indicated for only six out of 30 patients treated according to our protocol, while both patients who were treated with routine two-stage cranial vault expansion elsewhere required a third procedure. The risk factors for ICH in craniosynostosis syndromes include craniocerebral disproportion, venous outflow obstruction, moderate or severe OSA, and hydrocephalus.[17,19] In our cohort, OFC deflection after the first surgery occurred in 13 out of 32 patients, venous abnormalities in 17 out of 24, only one had ventriculomegaly, none had hydrocephalus, and moderate-to-severe OSA was detected in two out of 22. Of the six patients who underwent second surgery, five out of six had an OFC deflection, four out of four had venous abnormalities, one out of five had ventriculomegaly, and one out of three had moderate-to-severe OSA. Hence, craniocerebral disproportion (e.g. OFC deflection) and venous outflow obstruction due to an aberrant transverse sinus seem to be the main risk factors for ICH in patients with Saethre–Chotzen syndrome during follow-up. In contrast, moderate-to-severe OSA occurs less often than in other craniosynostosis syndromes, and polysomnographies should only be performed in case of anamnestic breathing difficulties. Whenever mild OSA is diagnosed, expectant care is advised (unpublished material, de Goederen et al.). In case of moderate-to-severe OSA, an adenotonsillectomy should be considered (unpublished material, de Goederen et al.).

The presence of venous anomalies in the majority of patients with Saethre–Chotzen syndrome could be related to the *TWIST1* gene mutation, since this mutation is involved in the development of vascular malformations of cerebral veins.[20] Venous anomalies such as an aberrant transverse sinus can limit the cerebral venous outflow as they result in abnormal venous drainage. After venous outflow obstruction, the increased hydrostatic pressure within the sinuses may eventually lead to ICH as it impairs the resorption of cerebrospinal fluid.[21,22] Emissary veins or venous collaterals have been regarded as an alternative venous pathway, and thus a compensation mechanism, for ICH by others.[19,21–23] The absence of a significant correlation between papilledema and emissary veins in our series might be correlated with the functional efficiency of these collateral veins.[21] Likewise, this finding highlights the presence of a complex interaction between causative factors for ICH in syndromic craniosynostosis.

A routine one-stage procedure seems to be sufficient to prevent ICH for the majority of the patients with Saethre–Chotzen syndrome. Therefore, we recommend a one-stage FOA for such patients. Whenever a second cranial vault surgery is indicated, occipital expansion or FOA should be performed, depending on the patients' phenotype.

Tonsillar herniation occurred in five patients. Four of these patients had an OFC deflection preoperatively;

however, only one developed papilledema. Moreover, none developed hydrocephalus and only one had ventriculomegaly, both of which are closely related to the mild tonsillar descent/Chiari type I malformation seen in Apert and Crouzon syndromes.[24] In a previous study, a normal volume of the cerebellum and posterior fossa was found in patients with Saethre–Chotzen syndrome[25] while brain volume was normal.[24] The mild herniation of cerebellar tonsils in these patients appears to be a result of restricted intracranial volume, and it appears to offer sufficient compensation to prevent progression into ICH. Additionally, the fact that eight out of the 12 patients with an OFC deflection did not develop tonsillar herniation matches the relatively mild impact of impaired skull growth in Saethre–Chotzen syndrome. MRI analysis of adult patients with Saethre–Chotzen syndrome would be valuable for further research, since the mean age at MRI was 6 years in our population and tonsil position is known to descend between the ages of 0 to 20 years.[26]

Comparing our Saethre–Chotzen cohort to those with other craniosynostosis syndromes, the prevalence of papilledema in this study seems to be higher than in patients with Muenke syndrome (23% vs 8% respectively).[10] This difference in prevalence might be caused by the absence of the four causative factors for ICH in Muenke syndrome.[10] In contrast, patients with Apert and Crouzon syndromes develop signs of ICH more frequently, which is probably caused by the higher prevalence of moderate-to-severe OSA, OFC deflection, and ventriculomegaly/hydrocephalus in these patients,[7,8,17,24,27,28] whereas the counts of venous anomalies in Apert and Crouzon syndromes seem to be comparable with Saethre–Chotzen syndrome.[22,23,29,30]

As with all investigations, this study has some limitations. First, the number of patients in this study prevented a trustworthy logistic regression model from being performed because of the small number of cases. With a larger sample size, a complete statistical model with all potential risk factors for ICH could be developed, and the precise contribution of these factors would be better clarified. Therefore, for future research purposes, a multicentre cohort study would be preferable. Second, patients underwent surgery performed by four different surgeons, which could potentially result in surgeon variability. However, we think that the influence of inter-surgeon variability was limited in our population because the surgical procedures performed were practically identical. Last, three out of the 32 patients were below the age of 6 years at the last follow-up, and were thus not followed up until skeletal maturity. Consequently, the reoperation rate that we recorded represents the lower bound, and is likely to vary between 20% to 30% (six out of 30 vs nine out of 30 patients who were treated according to the protocol).

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SUPPORTING INFORMATION

The following additional material may be found online:

Table S1: Overview of risk factors and ICH

Figure S1: OFC growth curve for patients with or without papilledema.

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