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Silent aspiration in infants with Prader–Willi syndrome identified by videofluoroscopic swallow study

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Abstract

Feeding intolerance in Prader–Willi syndrome (PWS) infants is well-recognized, but their swallow physiology is not well understood. Swallow dysfunction increases risks of respiratory compromise and choking, which have a high incidence in PWS. To investigate swallow pathology in PWS infants we undertook a retrospective review of videofluoroscopic swallow studies (VFSS) in infants with PWS seen at our institution. We hypothesize that VFSS will characterize swallow pathology suspected by clinical observation during a feeding evaluation and may help determine feeding safety in these infants.

Retrospective review of 23 VFSS on 10 PWS infants (average age 9.7 ± 8.4 months; range 3 weeks–29 months). Logistic regression models evaluated associations between gender, genetic subtype, and growth hormone (GH) use on aspiration incidence. Polysomnographic (PSG) studies conducted on the same participant ±1 year from VFSS were examined to characterize respiratory abnormalities.

There was a high rate of swallowing dysfunction (pharyngeal residue 71%, aspiration events 87%) and disordered sleep. All aspiration events were silent. There were no differences in rates of aspiration for gender, genetic subtype, or GH use.

A high incidence of aspiration was identified indicating swallow dysfunction may frequently be present in infants with PWS. Comprehensive evaluation of feeding and swallowing is essential and requires a multidisciplinary approach. Providers should recognize risk factors for swallow dysfunction and consider a multidisciplinary approach to guide decision making and optimize feeding safety in PWS.

Abbreviations: CSA = central sleep apnea, Del = deletion, F = female, GEE = generalized estimating equation, GH = growth hormone, IC = imprinting center defect, M = male, MBISmP = Modified Barium Swallow Impairment Profile, mUPD = maternal uniparental disomy, NC = not commented upon, OSA = obstructive sleep apnea, PSG = polysomnography, PWS = Prader–Willi syndrome, S/S/B = sucking, swallowing, and breathing, SCH = Seattle Children's Hospital, SDB = sleep disordered breathing, Undet = undetermined, VFSS = videofluoroscopic swallow studies.

Keywords: aspiration, dysphagia, Prader–Willi syndrome, videofluoroscopic swallow studies

1. Introduction

Prader–Willi syndrome (PWS), due to loss of expression from genes within the imprinted region at chromosome 15q11.2q13,[1] is associated with obesity after infancy.[2] The nutritional challenges in infants with PWS, however, center on feeding difficulties. These feeding challenges, often with accompanying hypotonia,[2] are described as a distinct nutritional phase (phase 1a),[3] during which feeding tubes for partial or full nutrition may be needed.[3,4] Currently, there are no specific guidelines to evaluate or manage feeding difficulties in infants with PWS.

Growth hormone (GH), approved by the Food and Drug Administration in 2000 for use in PWS, is offered as early as infancy.[5] GH started early in life is associated with improved motor development and strength.[6] However, no studies describing the impact of GH on feeding difficulties of infants with PWS have been published.

Swallowing impairments increase the risk of respiratory complications and choking, of which there is a high incidence in PWS.[7–9] There are also concerns with sudden death, potentially related to sleep disordered breathing (SDB).[10,11] Not coincidentally, swallowing abnormalities and SDB overlap as disturbances of both central neurologic control and peripheral upper airway muscle coordination. Despite numerous studies describing the use of objective measures such as polysomnog-

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raphy (PSG) to evaluate SDB,[12,13] relatively little has been reported on objective measures of swallow dysfunction, such as videofluoroscopic swallow studies (VFSS).

This study aims to characterize swallow dysfunction and risk of aspiration using VFSS in infants with PWS. We hypothesize that VFSS will characterize swallow pathology suspected by clinical observation during a feeding evaluation and may help determine feeding safety in these infants. With our findings, we propose a preliminary recommendation for evaluating and standardizing care for feeding dysfunction in infants with PWS.

2. Methods

We retrospectively reviewed records for children with PWS seen at Seattle Children's Hospital (SCH) who had completed at least 1 VFSS, obtained as part of clinical care. Using ICD-9 and 10 codes, we identified individuals with PWS seen at SCH from January 1, 1994 to July 30, 2016. Records were further reviewed to identify those who had undergone a VFSS. Demographic data, medical histories including genetic studies, use and timing of GH, and sleep and VFSS data were compiled. Sleep data consisted of PSGs that were obtained ±1 year from VFSS. The PSG temporally closest to VFSS were used for analysis if there were multiple PSG studies within that time frame. This study was approved by the SCH Institutional Review Board.

2.1. Videofluoroscopic swallow studies

All VFSS were clinically indicated due to observed feeding difficulties, following examination by a trained occupational therapist or speech therapist. Participants were observed swallowing a variety of standardized radiopaque contrast in consistencies ranging from thin liquids to pureed solids. Typical feeding implements were used with participants positioned in a Tumbleform feeder seat. Modifications to feeding position occurred if clinically indicated. Per SCH protocol, participants needed the ability to consume at least 20 mL of feeds orally in order to perform the VFSS. The Modified Barium Swallow Impairment Profile (MBISmP) was used to analyze swallowing function.[14] For this study, we defined aspiration as radiopaque material beyond the true vocal cords. VFSS results were classified as either demonstrating evidence of aspiration or no evidence of aspiration for any consistency tested (thin liquid, thickened liquid, pureed solids). External signs of aspiration (silent vs not silent) during the study were noted. Evidence of pharyngeal residue after swallow was also identified.

2.2. Polysomnography

PSG studies were performed at the SCH Sleep Disorders Center per standard protocol.[15] Data were recorded using a computer acquisition program (Natus Medical, Inc., Pleasanton, CA) and interpreted by a board certified Sleep Medicine physician in accordance with pediatric practice parameters of the American Academy of Sleep Medicine.[16] The Apnea-Hypopnea Index (AHI) was defined as the total number of respiratory disturbances averaged per hour of total sleep time and further divided into those caused by obstructive versus central events. Data were gathered on nadir oxygen saturations noted during PSG and considered abnormal if <90%.

2.3. Statistics

Data were stored using REDCap (Nashville, TN) and downloaded for statistical analysis. Descriptive statistics were performed for all outcomes. A logistic regression model with a generalized estimating equation (GEE) approach was used to evaluate effects of GH use, gender, and genetic subtype (deletion or nondeletion). Only participants with known genetic subtype were used in this evaluation. Statistical analysis was performed with STATA software (College Station, TX).

3. Results

3.1. Participants

There were 120 individuals with PWS identified and further reviewed for VFSS. We found 10 participants evaluated with VFSS at SCH at least once. Seven participants underwent more than 1 VFSS, for a total of 23 VFSS (Table 1). The average age at time of VFSS was 9.7 ± 8.4 months (range 3 weeks–29 months) with average age at time of first VFSS of 8.1 ± 8.4 months (range 3 weeks–27 months). Only 2/23 VFSS reviewed were conducted on participants on full oral feeds. Of the remaining studies, 12 were receiving full tube feeding (9 nasogastric, 3 gastrostomy) and 9 a combination of tube and oral feeds. All VFSS were conducted after 2003, and 74% (17) were done after 2012. Medications at time of VFSS are listed in Table 2.

Among the 10 participants, 60% were male and 40% were female. Deletion of the paternal PWS allele on chromosome 15 was detected in 5 of the participants (4 males, 1 female); 4 (2 males, 2 females) expressed a nondeletion subtype (uniparental disomy or imprinting center defect). One participant (female) had an undetermined genetic subtype (PWS methylation study diagnostic without subsequent testing).

3.2. Videofluoroscopic swallow studies

Aspiration on 1 or more VFSS was documented for 90% (9/10) of participants (Fig. 1). The 1 participant who did not exhibit aspiration had his only VFSS at 27 months old; therefore, we do not know whether he was aspirating at a younger age. Of all 23 VFSS reviewed, 87% (20) demonstrated aspiration with at least 1 trialed consistency. Reports from 21 VFSS commented on the presence of pharyngeal residue, and 71% (15) of these exhibited pharyngeal residue (Tables 1 and 3). The 3 VFSS that did not show aspiration also had no evidence of pharyngeal residue (participants 1, 3, and 6 at ages 7, 27, and 22 months, respectively). Two of these participants had prior VFSS which did indicate an aspiration event. All aspiration events noted on VFSS were silent.

Based on functional feeding level at the time of the VFSS, not all consistencies were examined during each study. It was noted that aspiration was inversely related to the consistency, with aspiration more likely with thin liquids (84%) than thickened liquids (60%) or purees (14%). The results for aspiration events by consistency, silent aspiration, and pharyngeal residue are shown in Table 3. There was no significant difference in aspiration between males and females (P = value .7) or between those with or without deletion subtypes (P = value .9).

3.3. Growth hormone

Five participants were on GH therapy at the time of at least 1 VFSS, and 43% of VFSS (10/23) were conducted while the participant was receiving GH. The average age of GH initiation in these PWS infants was 3.2 ± 1.6 months. All participants started GH at an initial dose of 0.5 mg/m^2/day and doses were titrated up to a max of 1 mg/m^2/day based on growth and goal

Table 1

Participant characteristics and clinical study results.

Subject	Gender	Subtype	Clinical indications for VFSS	Age* at VFSS	GH use at time of VFSS	Age* of GH start	Sleep disordered breathing (age* at time of PSG)	Aspiration	Pharyngeal residue
1	M	Del	Incoordination of S/S/B, multiple swallows to clear small volume	2	No	N/A	Undet	Yes	Yes
				7	No	N/A	Undet	No	No
2	F	Undet	Desaturations and bradycardia with oral feed	1	No	N/A	Undet	Yes	NC
				2	No	N/A	Undet	Yes	NC
3	M	Del	Cough and choking with feed	27	Yes	6	OSA (27)	No	No
4	M	mUPD	Incoordination of S/S/B, lethargy	1	No	N/A	Undet	Yes	Yes
				2	No	N/A	Undet	Yes	Yes
				6	No	N/A	Undet	Yes	No
5	F	IC	Incoordination of S/S/B, cough and desaturations with feed, fatigue with feed	0	No	N/A	OSA (2)	Yes	No
				3	Yes	2	OSA (2)	Yes	Yes
				7	No	N/A	OSA (4)	Yes	Yes
				10	Yes	7†	OSA (6)	Yes	Yes
				15	Yes	7†	OSA, CSA (13)	Yes	Yes
				21	Yes	7†	OSA, CSA (19)	Yes	Yes
6	F	Del	Choking on secretions	15	No	N/A	OSA (22)	Yes	Yes
				22	No	N/A	OSA (22)	No	No
				29	No	N/A	OSA (22)	Yes	No
7	M	mUPD	Tachypnea, hypotonia, inability to feed by mouth	14	No	N/A	OSA, CSA (10)	Yes	Yes
8	M	Del	Incoordination of S/S/B, increased respiratory effort with feed, multiple swallow attempts for small volume	6	Yes	3	OSA (5)	Yes	Yes
				10	Yes	3	OSA (11)	Yes	Yes
9	M	Del	Incoordination of S/S/B, fatigue with feed, hypotonia	7	Yes	3	OSA, CSA (6)	Yes	Yes
10	F	mUPD	Incoordination of S/S/B, hypotonia, congestion after feed, delayed gag reflex, lethargic	7	Yes	2	OSA (8)	Yes	Yes
				10	Yes	2	OSA (8)	Yes	Yes

CSA = central sleep apnea, Del = deletion, F = female, IC = imprinting center defect, M = male, mUPD = maternal uniparental disomy, NC = not commented upon, OSA = obstructive sleep apnea, PSG = polysomnography, S/S/B = sucking, swallowing, and breathing, Undet = undetermined, VFSS = videofluoroscopic swallow study.

* Ages expressed in months.

† Subject restarted GH treatment after held at 4 months old for worsening OSA.

Table 2

Medications at time of videofluoroscopic swallow study (VFSS).

Subject	Age* at VFSS	GH use at time of VFSS	Other medications at time of VFSS
1	2	No	None
	7	No	None
2	1	No	Ranitidine, amoxicillin, ferrous sulfate
	2	No	Ranitidine, amoxicillin, ferrous sulfate
3	27	Yes	None
4	1	No	Ranitidine
	2	No	Ranitidine
	6	No	Ranitidine
5	0	No	Multivitamin, ranitidine, phenobarbital
	3	Yes	Multivitamin, ranitidine, lansoprazole
	7	No†	Multivitamin, ranitidine, omeprazole
	10	Yes	Multivitamin, omeprazole, levocarnitine
	15	Yes	Multivitamin, omeprazole, levocarnitine, lactobacillus, ferrous sulfate
	21	Yes	Multivitamin, omeprazole, levocarnitine, lactobacillus, ferrous sulfate, coenzyme Q10, vitamin B complex
6	15	No	None
	22	No	None
	29	No	None
7	14	No	None
8	6	Yes	Cholecalciferol
	10	Yes	Cholecalciferol
9	7	Yes	None
10	7	Yes	Cholecalciferol
	10	Yes	Cholecalciferol, ranitidine

GH = growth hormone, VFSS = videofluoroscopic swallow study.

* Ages expressed in months.

† Subject restarted GH treatment after held at 4 months old for worsening OSA.

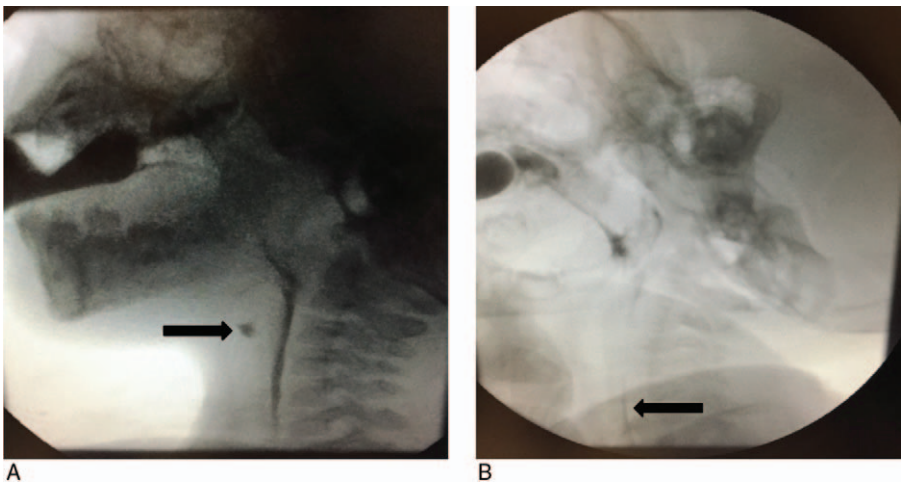

Figure 1. Images from a VFSS of an infant with PWS. (A) Aspiration during swallow. Contrast seen in the trachea (arrow); (B) pharyngeal residue after swallow. Swallowed contrast seen in the esophagus after swallow (arrow).

IGF-1 levels about +2 SDs. One participant (participant 5) had GH held between 4 and 7 months of age due to worsening OSA after initiation of GH. GH was restarted after surgical intervention and improved repeat PSG. One VFSS for this participant was done off GH while not GH-naïve. All other VFSS off GH in the study were GH-naïve. For VFSS done while a participant was on GH, 90% (9/10) showed aspiration of at least one texture, compared to 85% (11/13) of VFSS done off GH. Of the VFSS studies done while on GH therapy, 60% had pharyngeal residue. There was no significant difference in aspiration between those on or off GH (P = value .5).

3.4. Polysomnography

Seven of 10 participants had documented PSG within 1 year of VFSS, all of which were abnormal. All seven participants demonstrated obstructive sleep apnea. Three of these participants exhibited both obstructive and central sleep apnea (CSA), with one of these participants developing CSA over time. All PSGs showed abnormal nadir oxygen saturations. Five of the 7 participants had their PSGs done while on GH (see Table 1).

4. Discussion

To our knowledge, this is the first study to characterize aspiration using VFSS in infants with PWS. An abnormal VFSS, regardless of GH status, along with abnormal PSG were found in most participants. Notably, all aspiration events demonstrated on VFSS were silent. The VFSS confirmed suspicious clinical findings and was a useful tool to identify silent aspiration, the severity of which may not have been known with clinical observation alone. Without the findings from the VFSS, the extent of aspiration events may have been underdiagnosed or the implications of clinical feeding symptoms may have been minimized. Such results from VFSS can help identify necessary feeding modifications.

Infants with PWS demonstrate feeding difficulties related to the neuromuscular finding of hypotonia. Similar to other infants with neurologic and neuromuscular disorders, they may have a higher risk of feeding and swallowing dysfunction.[17] This may result from factors such as poor coordination of sucking, swallowing and breathing, weak oral musculature, or ineffective airway protection mechanisms.[18] Furthermore, there is an increased prevalence of dysphagia (23%) in children with developmental delays.[19] Infants and children with swallow dysfunction have a higher incidence of aspiration, choking, and respiratory illness compared to the general pediatric population.[3,7] We found high rates of swallow dysfunction and aspiration (87%) in our cohort. Under these circumstances, feeding safety is compromised, as these children may not be able to efficiently protect their airways while feeding. Silent aspiration is a concern since clinical signs, such as gagging or coughing, may not be observed.[17] Long-term respiratory sequelae of aspiration can occur, including lung damage.[20] Given the known hypotonia and developmental delays in PWS, our findings are not completely surprising. However, this high incidence of silent aspiration has not been previously reported in this cohort. As the infants in our cohort were referred for a feeding evaluation and VFSS because of a concern for aspiration, further studies are needed to confirm if these aspiration rates pertain to the general population of PWS infants and children.

We also investigated whether a relationship existed between the risk of aspiration and gender, genetic subtype, and the use of GH. Although we did not find a relationship between these variables and aspiration, a larger sample size may be needed to achieve significance and thus the effect on the risk of aspiration should be further explored. Swallowing is a complicated process

Table 3

VFSS results.

Aspiration by consistency, n (%)				
Thin liquid (N = 19)	**Thick liquid (N = 20)**	**Pureed solids (N = 14)**	**Silent aspiration (N = 20)**	**Pharyngeal residue (N = 21)**
16 (84%)	12 (60%)	2 (14%)	20 (100%)	15 (71%)

n = number of abnormal findings, N = total number of VFSS.

that requires the use of muscular and sensory mechanisms to orchestrate and coordinate the oral, pharyngeal, and esophageal phases.[7,17] GH has a known benefit to both tone and development in PWS, and could theoretically improve swallow function. In this study, there was no difference noted in the rate of aspiration in the GH treated participants, which may speak to the multifactorial nature of risk of aspiration in infants with PWS.

Recurrent aspiration can lead to pulmonary complications and lung injury.[21] Aspiration has also been associated with apparent life-threatening events in children.[22] Respiratory compromise in children with PWS is common. Mortality studies in PWS have found that respiratory illness in children, both infection and insufficiency, accounts for 61% of deaths in PWS children.[10] Deaths in infants with PWS are most likely to be related to respiratory failure, aspiration, infection, and choking.[23] In childhood, there is also a 17% reported incidence of sudden death in children with PWS >3 years old.[10] Choking is a known hazard, with 1 study reporting a 34% incidence and 8% mortality from reviewing deaths of 152 individuals with PWS (ages 3–52 years).[8] Other studies reported a 5% mortality due to choking in children with PWS, in comparison to a reported choking rate of 29.9 per 100,000 (~0.03%) in children <14 years in the United States.[10,24] Children with PWS clearly have an increased risk of respiratory morbidity, and it is quite possible that aspiration may increase risk.

Being a retrospective study, it is challenging to truly assess the pulmonary function of our participants and the effect of aspiration on their pulmonary status. To attempt to characterize pulmonary status at the time of VFSS, we reviewed temporally correlated PSGs. All had disordered sleep with evidence of sleep apnea and an abnormal oxygen nadir. This is consistent with previous studies which described SDB and abnormal nadir oxygen levels as common in infants with PWS.[12] Further studies are needed to determine whether a component of the abnormal respiratory findings in PWS during sleep is due to undiagnosed, chronic aspiration. Such longitudinal studies are needed to describe the relationship between aspiration and pulmonary morbidity.

A recently published study used VFSS to evaluate the effects of intranasal oxytocin on feeding in infants with PWS between 0.8 and 5.7 months of age.[25] This is the only other study to document VFSS results in infants with PWS. In this study they used a scoring system to evaluate abnormalities seen on VFSS before and after treatment with oxytocin. They commented that 13/16 infants exhibited pharyngeal stasis at baseline and overall VFSS scores improved after treatment. However, no comment was made regarding aspiration. Another study by Gross et al[26] used VFSS to investigate swallowing in 30 older participants with PWS (average age 18.6 years old, range 5–35 years). They found the majority of participants had disordered swallowing with pharyngeal residue (67% with liquids and 97% with solids), putting them at high risk of aspiration and choking. They also commented that participants were unaware of the pharyngeal residue and did not attempt to clear material unless asked. In this study, only 1 participant had aspiration, whereas in our younger cohort, all but 1 exhibited aspiration. One potential explanation is the difference in age, as our cohort was much younger. Interestingly, the child who did not have aspiration in our study had their first VFSS done at 27 months of age, which was one of the oldest ages at time of VFSS in our review. The other 2 children who had a VFSS without aspiration had a previous VFSS that did demonstrate aspiration. It may be that swallow dysfunction and aspiration risk change over time.[21] It is noteworthy that both studies show a high rate of pharyngeal residue, which has been linked to higher risk of aspiration. As neither of our studies followed the course of swallow function over time, further longitudinal studies are needed to better describe the natural history of swallow dysfunction and risk of aspiration in PWS. Unfortunately, data on baseline prevalence of pharyngeal residue in infants and children with PWS is lacking as studies evaluating VFSS results have thus far been done only in children with feeding difficulties. Therefore, it is challenging to assess if the described aspiration rates are abnormally elevated compared to the general PWS population. With the demonstrated high risk of choking in the PWS population, however, it is important that we not disregard this data.

Our study has a number of limitations, the first being sampling bias. We are an academic center where complex patients are referred, and therefore we may have seen individuals with more serious clinical findings. In addition, all children who underwent VFSS had clinical indications of feeding difficulties. It should be noted, however, that our center is the only PWS clinic that provides multidisciplinary care for children with PWS in our area, and consequently we have a wide spectrum of severity in our patients. In addition, it is well known that infants with PWS have feeding difficulties, so the majority actually have clinical indications to undergo a formal feeding evaluation and subsequent swallow study. It is noteworthy that all infants seen in our PWS clinic in the last 2 years have received VFSS for clinical indications, and that the majority of reviewed studies were conducted after 2012 despite the fact that VFSS have been available at our institution for over 20 years. The increased use of VFSS in recent years reflects an evolution in the management of PWS infants at SCH over time with expanded multidisciplinary treatment and protocols that incorporate investigative tools such as the VFSS in the determination of feeding care. Based on our experience in evaluating infants with PWS, the need for a formal swallow evaluation should be the norm rather than the exception.

Another limitation is the small sample size and the retrospective nature of our present study. Larger longitudinal prospective studies are needed to further demonstrate the natural evolution of swallow dysfunction in children with PWS, and to explore the causal relationship between respiratory morbidity and risk of aspiration. Our pilot study is not yet able to provide definitive conclusions on the prevalence of swallow dysfunction or on a causal relationship between aspiration and respiratory morbidity. These preliminary data do indicate that abnormalities exist that need to be further explored.

4.1. Comprehensive feeding/swallowing management

Despite the use of various feeding interventions and GH during infancy, feeding problems among PWS infants remain high. To help individualize and direct care, it would therefore be ideal to establish proper diagnosis of pathologic feeding and swallowing abnormalities in infancy. Thus, unless future studies demonstrate otherwise, we recommend that all PWS infants undergo a comprehensive feeding/swallowing evaluation using a multidisciplinary approach whenever possible. When the full extent of feeding and swallowing pathology is understood, referrals for appropriate interventions can occur.

This retrospective review assessed swallow dysfunction and risk of aspiration in infants from birth to 29 months with PWS and a concern for feeding dysfunction. We found a high rate of silent aspiration and pharyngeal residue in our cohort. This is the first study to describe swallow dysfunction and aspiration in

infants with PWS by VFSS rather than relying solely on clinical observation. Further longitudinal studies are needed to characterize swallow in PWS over time. Particularly important is gaining an understanding of the prevalence of swallow dysfunction, the time frame for and resolution of disordered swallowing, and whether this is observed only in infants and young children or is a lifelong complication of PWS. A comprehensive, multidisciplinary approach to evaluation of feeding/swallowing will ensure that all relevant issues are identified and appropriate interventions implemented.

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