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RESEARCH REPORT

Quality of Life in Adult Patients with Glycogen Storage Disease Type I: Results of a Multicenter Italian Study

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Abstract Background: Glycogen storage disease type I (GSD I) is a chronic metabolic disease that requires a lifelong strict dietetic treatment to avoid hypoglycemia and can lead to severe complications during adult age. Impaired quality of life (QoL) has been reported in affected children, but this aspect has not been previously investigated in adults.

Objective: To assess QoL in adult patients with GSD I.

Patients and Methods: Italian patients with GSD type Ia and Ib, who were 16 years or older, were asked to complete the SF-36 questionnaire, assessing their QoL. Data on demographic characteristics and clinical history were collected from clinical records and interviews.

Results: Thirty-eight patients (22 females, 16 males; 27 with GSD Ia, 11 with GSD Ib, median age 26.5 years) completed the SF-36 questionnaire. Overall, when compared to normal values, patients with GSD I had lower median scores in *general health perception* and *social functioning,* but better median scores for *bodily pain* and *mental health*. Patients with GSD Ib had a lower Z-score than GSD Ia patients for *emotional health problems*. Male patients showed better Z-scores in *physical functioning*, *general health perception,* and *social functioning* when compared to females. *Emotional health problems* Z-score was lower in nephropathic patients.

Conclusion: QoL can be impaired in adult patients with GSD I. The results of this study show that patients with GSD type Ib, women, and those with renal complications are more likely to experience a poorer QoL.

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Introduction

Glycogen storage disease type I (GSD I) is a rare inherited metabolic disease affecting carbohydrate metabolism. Two variants of the disease have been clinically and genetically distinguished: GSD Ia, due to defects of the glucose 6-phosphatase (G6Pase) hydrolytic enzyme (coded by the G6Pase gene, band q21 chromosome 7); and GSD Ib, due to defects of the glucose G6P transporter (coded by the G6P translocase gene, band q23 chromosome 11) (Chen 2001). Both forms are rare conditions, considering that the estimated prevalence of GSD (types I–IV) is about 0.00004 %, but GSD Ib is less frequent, representing about 20 % of GSD type I (Wolfsdorf and Weinstein 2003).

GSD Ia is characterized by hypoglycemia (induced by a short fasting period), hyperuricemia, hyperlipidemia, hepatomegaly, truncal obesity, and bleeding tendency (Rake

et al. 2002a). GSD Ib shares its main features with GSD Ia, but it is also characterized by neutropenia and neutrophil dysfunction, associated with frequent infections and possible chronic inflammatory bowel disease (Visser et al. 2000). Furthermore, long-term complications such as chronic anemia, kidney disease, arterial hypertension, hepatic adenomas with a small risk of malignant transformation, osteopenia, and, rarely, pulmonary hypertension may occur in both types (Talente et al. 1994).

The disease generally presents during early infancy (Rake et al. 2002a) and the main treatment is lifelong diet therapy, consisting of frequent meals, rich in complex carbohydrates in order to avoid hypoglycemic episodes and secondary metabolic derangements. Fasting tolerance is variable among patients, and it may be different according to age. However, affected subjects are usually forced to eat every 3–4 h during daytime, and to consume uncooked cornstarch (UCCS) before going to bed, or to use continuous nocturnal gastric drip feeding (CNGDF) to prolong sleep time (Rake et al. 2002b; Visser et al. 2002).

In modern medicine, it has become more accepted that the aims of medical care should not only be to alleviate the physical symptoms of the disease but also to improve the overall quality of life (QoL). In GSD I, QoL can be impacted by the disease and its complications, by the strict diet regimen and the eventual medications, and by the medical procedures needed in a comprehensive follow-up, such as blood samples, ultrasounds, magnetic resonances, and bone densitometry. A reduced QoL has been previously demonstrated in children affected by GSD Ia and Ib (Storch et al. 2008).

Life expectancy in GSD I is still undefined, but it has dramatically improved, compared to 30 years ago, with more and more patients surviving to adulthood (Martens et al. 2008). As a consequence, patients have to deal with new issues connected with self autonomy, integration into society, traveling, competitive working, and having a family of their own. In this context, investigating QoL in adult GSD I patients is of particular interest, but, to our knowledge, no data are available so far on this topic. Therefore, a cross-sectional study was conducted in order to depict a profile of the QoL of adult patients affected by GSD I and to identify possible groups at higher risk of a low QoL.

Methods

Patients affected by GSD type Ia or Ib were enrolled between 2009 and 2012 in seven different Italian metabolic centers. Diagnosis had to be confirmed by enzyme assay on hepatic biopsy or by molecular analysis. Patients with a liver or kidney transplant or on a waiting list for transplantation were excluded. A written informed consent was obtained from all participants.

Information on sociodemographic characteristics and clinical history were gathered both from clinical records and face-to-face interviews. Clinical records were reviewed to retrieve information on anemia (Hb $<$ 12 g/dl for males and Hb $<$ 11 g/dl for females), hepatic adenomas (identified through ultrasound scan or MRI), hypertension (defined as blood pressure repeatedly $>$140/90 mmHg or use of antihypertensive drugs for hypertension treatment), microalbuminuria (defined as albumin excretion 30–300 mg/24 h), proteinuria (defined as albumin $>$300 mg/24 h or protein $>$ 150 mg/24 h and diagnosed from a 24-h urine collection), chronic renal failure (CRF, defined as a glomerular filtration rate (GFR) $<$ 60 ml/min), and chronic inflammatory bowel disease (IBD, defined as the presence of perianal infection and protracted diarrhea).

Health-related QoL was assessed through the Italian version of the Short Form Health Survey (SF-36) questionnaire. This toll has been validated in several experimental and observational studies regarding different chronic diseases and has been widely used in clinical studies involving Italian subjects since 1990 (Apolone et al. 1997). The SF-36 questionnaire consists of 36 items combined into eight scaled scores: *physical functioning*, *role physical* (limitations caused by physical health problems), *bodily pain*, *general health* perception, *vitality*, *social functioning*, *role emotional* (limitations caused by emotional health problems), and *mental health*.

The raw score of each scale was transformed into a 0–100 scale and then normalized to a Z-score using normative Italian data. The physical and mental component summary measures (PCS and MCS, respectively) are also computed and transformed to norm-based scores (mean = 50, standard deviation = 10) using the mean, standard deviation, and scoring coefficients from the US general population (Ware and Sherbourne 1992). Both for combined scales and summary measures, higher scores indicate more favorable physical functioning or psychological well-being.

Statistical Analysis

The standard SF-36 protocol was applied to perform the analyses of SF-36 questionnaires (Apolone et al. 1997; Ware and Sherbourne 1992). Briefly, after checking for out-of-range answers, missing values were replaced by scale means where valid responses were available for at least half of the scale items. Scores were then recoded, recalibrated, and converted into 0–100 scores. Finally, summary measures were computed using the US population normative values (Ware and Sherbourne 1992) since these provide reliable estimates even when applied to non-US populations (Apolone et al. 1997).

All categorical variables are described as frequencies and percentages, while median and interquartile ranges are reported for continuous variables. The rank sum test was used to compare the QoL scores in different groups.

The statistical software Stata 11.0 (Stata Statistical Software: Release 11.0, 2009. StataCorp LP, College Station, TX, USA) was used to perform data analysis.

Results

Thirty-eight GSD I patients were enrolled, and their general characteristics are reported in Table 1. All were Caucasians. Two patients were sisters, while the others belonged to different families. Their median age was 26.5 years, the youngest being 16 and the oldest being 41. Their median age at diagnosis was 1 year, the earliest diagnosis being made at about 2 months of age and the latest at 24 years.

Most of the patients ($n = 27$) were affected by type Ia GSD, while 11 had type Ib. Their clinical relevant characteristics are described in Table 2. As regards comorbidities, one female patient had suffered from epilepsy since childhood, two males had a history of nephrolithiasis, one female had pulmonary hypertension, and two males with GSD Ib had chronic inflammatory bowel disease. One female with GSD Ib had autoimmune hypothyroidism. A disturbance of alimentary behavior was signaled in one female patient, but no other psychiatric problems were reported.

At the study time, all patients were following a diet consisting of frequent meals rich in complex carbohydrates, with variable restrictions in lactose or fructose intake, and were taking UCCS at least once a day. Detailed data on UCCS consumption were available for 32 patients. The median UCCS dosage was 120 g/day (interquartile range [IQR] 100–160; range min–max 40–325), considering patient's weight the median dosage was 1.9 g/kg/day (IQR 1.5–2.5; range min–max 1–5.1), the majority of patients assuming it twice a day (range min–max 1–6). Nine out of 32 patients (28.1 %) were forced to wake up during nighttime, interrupting sleeping, to take a dose of UCCS.

Three patients out of 38 were also using continuous nocturnal gastric drip feeding (CNGDF), while another 12 used CNGDF during childhood, but stopped it in adulthood. Thirty-five patients were taking medications; the detailed drug consumption is shown in Table 3.

Thirty-four respondents completed all SF-36 items, while four participants, all females, had at least one missing SF-36 item. In two cases, it was possible to input all missing values (1 in *physical functioning,* 1 in *mental health*, 1 in *general health*), in one the imputation could be made only for one *bodily pain* item but not for *role physical* and *role emotional* (all items were missing), and in another one *physical functioning* scale could not be calculated since all the items were left blank.

Table 1 General characteristics of the patients ($n = 38$)

	n	%	Median	Interquartile range
Gender				
Male	16	42.1		
Female	22	57.9		
Age (years)			26.5	20–32
Age at diagnosis (years)			1	0.4–3
Age at diet therapy start (years)			3	1–9
Education[a]				
Junior high school	12	34.3		
Senior high school	20	57.1		
University	3	8.6		
Occupation[a]				
Employed	18	51.4		
Unemployed	4	11.4		
Student	11	31.4		
Housewife	2	5.7		
Marital status[b]				
Unmarried[c]	33	86.8		
Married	5	13.2		
With one child	3			
With two children	2			

[a] Three patients did not report their educational level nor their occupation.

[b] There were no separated, divorced, or widowed people.

[c] No unmarried subjects had children.

The transformed scores for each scale are reported in Table 4, while Table 5 shows the SF-36 Z-scores.

Overall, *physical functioning*, *role physical*, *vitality*, and *role emotional* scores were consistent with the Italian reference values, while GSD I patients scored better in *bodily pain* and *mental health* scales and worse in *general health* and *social functioning* (Table 4).

Summary measures for both physical and mental component were consistent with normal US values (Table 4).

When a stratified analysis was performed by gender, males showed better scores in *physical functioning* (95 vs. 85; Z-scores 0.45 vs. 0.02; $p = 0.002$), *general health* (72 vs. 52; Z-scores 0.31 vs. −0.60; $p = 0.01$), and *social functioning* (94 vs. 69; Z-scores 0.70 vs. −0.37; $p = 0.03$). Furthermore, when differences were investigated according to GSD I type, *role emotional* showed to be much better

Table 2 Clinical characteristics of the patients ($n = 38$)

	n	%
Type		
Ia	27	71.1
Ib	11	29.0
Anemia	20	52.6
Adenomas	16[a]	42.1
Microalbuminuria	11	29.0
Proteinuria	9	23.7
Chronic renal failure	1	2.63
Hypertension	5	13.2
UCCS	38	100
CNGDF, ongoing	3	7.9
CNGDF, ever	15	39.5
Drug consumption	35	92.1
Number of drugs[b] (only patients assuming drugs, $n = 35$)	1	2–4

UCCS uncooked cornstarch, *CNGDF* continuous nocturnal gastric drip feeding

[a] Among these, two patients underwent to surgical resection (because of adenoma's diameter >5 cm)

[b] Median (interquartile range)

Table 3 Drugs consumed by the patients ($n = 38$)

Drug	Number of patients
Allopurinol	34
ACE inhibitor or Sartan	16
Calcium	9
RHGCSF	7
Iron	7
Multivitamins	6
Omega 3	4
Mesalazine	2
Antidepressant	0
Anxiolytic	0
Other[a]	5

RHGCSF recombinant human granulocyte colony-stimulating factor

[a] Anticonvulsants (1), furosemide (1), levotiroxine (1), fibrate (1), anti-inflammatory drugs (1)

in patients affected by GSD type Ia when compared to patients affected by GSD Ib (100 vs. 33; Z-scores 0.64 vs. −1.15; $p = 0.01$) (Table 5). Moreover, patients with renal complications (at least one of either microalbuminuria, proteinuria, or chronic renal failure) showed a worse *role emotional* than patients with unaffected kidneys (83.3 vs. 100; $p = 0.04$), while no differences were found according to anemia, hepatic adenomas, age (≤20 vs. >20 years), age at diagnosis (<3 vs. ≥3 years), age at diet therapy start (<3 vs. ≥3 years), UCCS dosage or timing, and CNGDF use (data not shown).

Discussion

GSD I is a rare metabolic disease that may result in different dysfunctions and long-term complications, and requires the adoption of specific dietary habits to avoid metabolic drawbacks. As a consequence of both the disease itself and of its treatment, affected patients may experience an impairment of their QoL, this being a multidimensional concept reflecting the patient's subjective evaluation of his/her functioning and emotional well-being. Investigating QoL is important to discover possible shortfalls in the management of patients, especially those with a chronic disease that is likely to have a long-term impact on all aspects of everyday life. Nevertheless, to our knowledge, this is the first study investigating QoL among adult patients with GSD I since this aspect was investigated only in children so far (Storch et al. 2008).

Social outcome (including interpersonal relationships, education, and professional carrier) is strictly linked with QoL, and it has been previously demonstrated that in inborn errors of metabolism impaired QoL can be associated with an altered social structure in comparison to healthy peers (Simon et al. 2008). Although QoL was not one of the aims of the study, the European Study on GSD I (ESGSD I), conducted on more than 200 GSD I patients reported that 11 % needed a special education or work, while 6 % were unable to have a profession because of mental disability (Rake et al. 2002a). In contrast, in our cohort, neither mental disability nor need for special education or work was reported. In fact, 20 patients had a senior high school diploma and 3 held a university degree. Moreover, 18 patients had a normal employment and 11 were students in normal schools or universities. However, it must be kept in mind that the ESGSD study was conducted in 2002, and many adult patients from this cohort had treatment pre-dating the use of UCCS during their childhood, hence several had probably poorer metabolic control at the time of their growth. The current standards of care prevent patients from suffering severe hypoglycemia during childhood, thus avoiding brain damage (Wolfsdorf and Crigler 1999) and allowing patients to have a regular education and job.

The present study showed that overall GSD I adult patients had lower scores in *general health* perception and *social functioning*.

The personal evaluation of *general health* given by GSD I patients was similar to that reported by patients affected by type 2 diabetes, another chronic disease requiring a lifelong diet (Lloyd and Orchard 1999). This suggests that the implications of the disease and its treatment on everyday life

Table 4 SF-36 scores

	Score	Reference
Scaled scores (0–100)	**Median (IQR) (range min–max)**	**Median (range min–max)**[a]
Physical functioning ($n = 37$)	95 (85–95) (0–100)	95 (0–100)
Role-physical ($n = 37$)	100 (75–100) (0–100)	100 (0–100)
Bodily pain ($n = 38$)	100 (62–100) (20–100)	84 (0–100)
General health ($n = 38$)	57 (47–72) (5–100)	70 (0–100)
Vitality ($n = 38$)	60 (45–75) (25–90)	65 (0–100)
Social functioning ($n = 38$)	75 (63–100) (37.5–100)	87.5 (0–100)
Role-emotional ($n = 37$)	100 (67–100) (0–100)	100 (0–100)
Mental health ($n = 38$)	80 (56–92) (28–96)	68 (0–100)
Summary measures	**Median (IQR)**	**Median (IQR)**[b]
Physical component ($n = 36$)	50.8 (45.8–55.7) (31.1–59.8)	53.3 (45.2–57.1)
Mental component ($n = 36$)	49.1 (39.3–57.6) (30.9–60.9)	49.3 (40.6–54.3)

[a] Reference: Italian population

[b] Reference: US population

have a stronger impact on the general well-being perception than the disease itself. Thus, even a very rare and a common disease may share similar scores in *general health*.

Social functioning represents the extent to which physical health or emotional problems interfere with normal social activities. Low scores found in GSD I patients can be explained with the need for frequent meals at scheduled times that may prevent affected adults from being flexible and adapting to the fast rhythm of the contemporary society. Furthermore, these patients need to restrict simple sugars, fat and alcohol intake, resulting in a diet that is different from their peers'. This can limit or even hamper many social activities, such as going out for dinner or participate in a party (Bhattacharya 2011).

Interestingly only 13.2 % patients among our cohort were married and had children, while the expected percentage would be 25.3 % (95 % CI 15.4–37.3), when the age- and gender-matched Italian population is used as a reference (Istat, Italian National Institute of Statistics www.istat.it). These data might reflect the lower scores in social functioning, with probably more difficulty in forming adult relationships in which to have children than healthy peers. Furthermore, difficulty in becoming independent from parents and starting their own family has been observed in people with inherited metabolic diseases in general. Considering the high level of parental involvement in disease management during childhood, this is not unexpected (Lee 2002).

Interestingly, adult patients with GSD I showed better scores than the general population in *bodily pain* and *mental health* scales. This can be explained by the coping phenomenon, thanks to which people with a chronic illness are able to emphasize the positive aspect of their lives, to reduce the general stress (Carver and Connor-Smith 2010), although we cannot exclude that participants were hesitant to report difficulties in these areas.

Compared to the study published by Storch and colleagues, describing a lower QoL in several areas and summary measures in youth GSD I patients (Storch et al. 2008), we found generally better results for adult patients, with the summary measures for physical and mental components being within the normal range. This difference between adults and children can have different interpretations. First of all, during adulthood the exogenous glucose amount required to maintain normoglycemia is lower than that during growth; as a consequence, fasting time can usually be prolonged, allowing patients both to have less frequent meals during the day and longer sleep periods (Moses 2002). In fact, in our cohort, many patients used CNGDF during childhood but were able to stop it during adulthood when the consumption of cornstarch was sufficient to achieve a good glycemic control during the night.

Secondly, having a chronic disease since early childhood can promote the development of an adaptive behavior in which adult patients, through years of experience with their disease, are able to use strategies (i.e., always carrying some food in their bags or consuming extra cornstarch before physical activity) that allow them to participate in normal activities (such as working, playing sports, or traveling), as well as their healthy peers.

Interestingly, in the study by Storch and colleagues, a high level of parental stress was found, and parents generally felt that their children were more impaired than reported by the children themselves. Most likely, this parental attitude negatively affects the QoL during childhood, while parental stress has probably a lower influence in adulthood, with a positive effect on QoL.

Table 5 SF-36 Z-scores

Scales	All *Median (IQR)*	Males *Median (IQR)*	Females *Median (IQR)*	p Value	Type Ia *Median (IQR)*	Type Ib *Median (IQR)*	p Value
Physical functioning	0.45 (0.02;0.45) $n = 37$	0.45 (0.45;0.67) $n = 16$	0.02 (−0.62;0.45) $n = 21$	0.002	0.35 (0.02;0.45) $n = 26$	0.45 (0.02;0.45) $n = 11$	0.92
Role-physical	0.61 (−0.09;0.61) $n = 37$	0.61 (0.61;0.61) $n = 16$	0.61 (−0.09;0.61) $n = 21$	0.22	0.61 (−0.09;0.61) $n = 26$	0.61 (−0.09;0.61) $n = 11$	0.42
Bodily pain	0.95 (−0.42;0.95) $n = 38$	0.95 (−0.39;0.95) $n = 16$	0.95 (−0.46;0.95) $n = 22$	0.91	0.95 (−0.46;0.95) $n = 27$	0.95 (0.37;0.95) $n = 11$	0.42
General health	−0.37 (−0.82;0.31) $n = 38$	0.31 (−0.15;0.60) $n = 16$	−0.60 (−1.27;−0.15) $n = 22$	0.01	−0.37 (−0.82;0.53) $n = 27$	−0.46 (−1.72;0.31) $n = 11$	0.29
Vitality	−0.09 (−0.82;0.63) $n = 38$	0.03 (−0.57;1.00) $n = 16$	−0.21 (−1.01;0.39) $n = 22$	0.29	0.15 (−0.82;0.63) $n = 27$	−0.57 (−1.30;1.12) $n = 11$	0.63
Social functioning	−0.10 (−1.71;0.97) $n = 38$	0.70 (−0.10;0.97) $n = 16$	−0.37 (−1.18;0.97) $n = 22$	0.03	−0.10 (−0.64;0.97) $n = 27$	−0.10 (−0.64;0.97) $n = 11$	0.75
Role-emotional	0.64 (−0.25;0.64) $n = 37$	0.64 (−0.25;0.64) $n = 16$	0.64 (−0.25;0.64) $n = 21$	0.35	0.64 (0.64;0.64) $n = 26$	−1.15 (−1.15;−0.64) $n = 11$	0.01
Mental health	0.64 (−0.51;1.22) $n = 38$	0.64 (−0.32;1.22) $n = 16$	0.35 (−1.08;1.02) $n = 22$	0.22	0.64 (−0.51;1.22) $n = 27$	0.07 (−0.70;1.22) $n = 11$	0.90

To explain the good summary measures found, we also need to consider that the present study was conducted in Italy, a country where the GSD nutritional requirements can easily match the common diet, rich in complex carbohydrates. Thus, we cannot exclude that a similar evaluation performed in other countries, where food habits are very different and not consistent with a GSD diet, could give different results.

Moreover, we also cannot exclude that there was a difference in disease severity between the two study populations since 10/38 patients in our cohort were diagnosed after 2 years of age, probably due to a mild disease. Unfortunately, no data about disease history were present in the Storch study. Finally, we must point out that the two studies are not fully comparable since different tests were used to assess QoL due to the different age of participants (Pediatric Quality of Life Inventory version 4.0 in the study by Storch and colleagues vs. SF-36 in the present study) (Storch et al. 2008). In spite of low numbers, we also tried to perform several stratified analyses and to compare different subgroups of patients. As a result, we found that patients with GSD type Ib reported lower values than type Ia. This can be explained clinically since GSD Ib subjects often suffer from frequent infections and bowel disease, which can affect everyday living (Froissart et al. 2011). However, interestingly, in our cohort, we found a lower rate of IBD than that in the ESGSD study (18 % vs. 77 %) (Visser et al. 2002). The reason could be that in our cohort 7/11 GSD Ib patients were receiving recombinant human granulocyte colony-stimulating factor, and this treatment could have reduced the proportion of patients affected by IBD.

Lower QoL was also found in patients with renal complications (microalbuminuria, proteinuria, or chronic renal failure). Only one patient suffered from chronic renal failure and this condition can be easily associated to a poorer QoL; on the other hand, those suffering from microalbuminuria or proteinuria usually take additional drugs, and this treatment probably strengthens the patient's consciousness of having a kidney disease that can progress further, thus affecting the QoL.

Moreover, female patients reported lower scores than males in several scales, irrespective of the differences in GSD type, number of complications, or number of drugs taken. This could be related to a gender difference in experienced stress. In particular, woman can be more concerned about their physical appearance, which can be altered by a prominent abdomen, a characteristic face, and, sometimes, by a short stature (especially the old generation). Furthermore, women can be more anxious about their health, and this can affect the perceived well-being.

As liver transplantation is thought to ameliorate GSD I patients' QoL, overcoming the problem of recurrent hypoglycemia and the necessity of a strict diet (Kido et al. 2013), it would be of interest to assess the difference between GSD I patients medically treated and those who underwent hepatic transplantation through a validated instrument of QoL assessment. Anyway, in Italy very few GSD I patients

underwent liver transplantation so far to allow a sufficient sample size to perform a comparison. Since transplantation completely changes the disease burden, transplanted patients were excluded from this study by design.

Conclusions

QoL can be impaired in adult patients with GSD I; therefore, the evaluation of QoL using validated scales should be included in their periodic follow-up. Particular attention should be paid to patients with GSD type Ib, women, and those suffering from renal complications since they are more likely to experience a poorer QoL.

QoL improvement should be one of the aims of the disease management. The development of new treatments (i.e., long-lasting starches, gene therapy) might ameliorate QoL of GSD I patients in the future.

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Compliance with Ethics Guidelines

All authors declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

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