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Prevalence of chromosomal abnormalities in 2078 infertile couples referred for assisted reproductive techniques

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BACKGROUND: This study analyses the prevalence of karyotype changes and Yq11 microdeletions among couples referred for assisted reproduction techniques. METHODS: Prior to receiving either IVF or ICSI treatment, each partner of 2078 infertile couples was screened for karyotype changes by GTG-banding technique on peripheral lymphocytes. No subject presented with obvious phenotype of chromosomal rearrangement. All the oligo/azoospermic men with normal karyotype were further investigated by PCR for Yq11 microdeletions. RESULTS: Eighty-two out of 2078 couples (3.95%) had one partner carrying a chromosomal change, and 10 out of 202 (4.95%) men showed Yq11 microdeletions. The chromosomal rearrangements were 44 (2.1%) translocations, 23 (1.1%) gonosomal mosaics, six (0.3%) 47,XXY, five (0.24%) marker chromosomes, three (0.14%) inversions and one (0.05%) duplication. Frequency of anomalies in men and women were similar: 42 and 40 cases respectively. CONCLUSIONS: Partners of infertile couples requiring IVF or ICSI treatment appear to be affected by higher frequency of chromosomal rearrangements than the general population. Categories with greater risk were represented by men with sperm cell count $<20 \times 10^6$ sperm/ml, and women with history of pregnancy loss.

Key words: assisted reproduction techniques/chromosomal aberration/infertility/Yq11 microdeletion

Introduction

Constitutional aberrant karyotypes can account for infertility or recurrent pregnancy loss. When present in the germinal lineage, chromosomal abnormalities can be segregated in gametes and transmitted to the offspring, while in other cases they can hamper meiosis up to the arrest of gametogenesis, or may give rise to unbalanced gametes (Makino *et al.*, 1990; McFadden and Friedman, 1997; Wilkins-Haug *et al.*, 1997; Lawler and Gearhart, 1998; Pao-Lin Kuo, 2002; Gekas *et al.*, 2003). In mammals, gametes carrying chromosomal aberrations have a poor chance of successfully undergoing fertilization. Natural selection of cells with integer genome usually prevents the formation of zygotes with major abnormalities. A concern about assisted reproductive techniques is that they might force the formation of a zygote overriding hidden chromosomal changes in parents, thereby propagating genetic anomalies to the next generation (Engel *et al.*, 1996). With the introduction of ICSI, concern about a possible increase in the rate of early miscarriages or fetal malformations owing to parental genetic anomalies has increased (Hargreave *et al.*, 1998; Bonduelle *et al.*, 2002).

The present study offers our contribution on the topic by a retrospective analysis of the prevalence of chromosomal abnormalities in a population of infertile Italian couples attending assisted reproduction programmes.

Materials and methods

Clinical files of 2078 infertile couples, referred during January 1995 to December 2003 to receive treatment by either IVF or ICSI were reviewed in this study. All cases were white Caucasians from the central regions of Italy. The cytogenetic analysis was routinely applied to all the couples undergoing assisted reproduction treatment.

Investigation for chromosomal anomalies was routinely performed by cytogenetic analysis of both partners of each couple. The karyotypes were performed by GTG-banding technique studying ≥ 20 metaphases of proliferating lymphocytes from peripheral blood. In any case of rearranged karyotype in mosaic form, due to the presence of one or more non-modal cells, ≥ 50 metaphases were examined, and when required other banding techniques or spectral karyotyping (SKY) and fluorescence *in situ* hybridization (FISH) were used. Structural and numerical autosome aberrations were defined on the basis of at least three metaphases, while gonosome mixoploidies were considered only when non-modal cells were present in $>8\%$ of metaphases (Scholtes *et al.*, 1998; Sonntag *et al.*, 2001). Chromosome polymorphisms such as changes in size of heterochromatin regions and pericentric inversions of chromosome 9 were not considered. All the men affected by severe oligozoospermia or azoospermia had a normal karyotype were further investigated for the presence of microdeletions of the three AZF loci in Yq11 (AZFa, AZFb and AZFc) (Stuppia *et al.*, 1996; Foresta *et al.*, 2001). Azoospermia, severe oligozoospermia and mild oligozoospermia

were defined as the total absence of sperm cells in seminal liquid, a sperm cell count $\leq 5 \times 10^6$ cells/ml, and a sperm cell count $> 5 \times 10^6$ and $< 20 \times 10^6$ cells/ml respectively. Each diagnosis of oligo/azoospermia was achieved by at least two consecutive spermiograms performed in ejaculated semen after centrifugation of the specimens.

The search for microdeletions was carried out by amplifying, with PCR, 10 sequence-tagged sites (STS) encompassing the AZFa, AZFb and AZFc loci, according to the reported guidelines (Simoni *et al.*, 2004).

Differences between proportions were assessed by χ^2-test ($P \leq 0.05$).

Table I. General features of the studied population

No. of couples	2078
Age of women (years)	34.03 ± 4.72 (20–48)[a]
Age of men (years)	36.92 ± 5.66 (23–66)[a]
Duration of infertility (years)	4.66 ± 3.48 (1–20)[a]
Couples with history of:	
gravidity ≥ 1, parity = 0	923 (44.42)[b]
gravidity = 0, parity = 0	1155 (55.58)[b]

[a]Mean ± SD (range).
[b]*n* (%).

Results

The general features of the studied population are summarized in Table I, while Tables II–V document the prevalence of the chromosomal changes found in the whole sample.

A total of 1155 couples out of 2078 studied (55.6%) never achieved pregnancy, namely each female partner had history of gravidity = 0 and parity = 0 (G0P0 group); the remaining 923 (44.4%) had history of at least one spontaneous pregnancy loss within the 12th gestation week, namely each female partner had gravidity ≥ 1 and parity = 0 (G≥ 1P0 group).

Considered as a whole, in this cohort of 4156 subjects, i.e. 2078 men and 2078 women, we found 82 chromosome aberrations, corresponding to one case of chromosome anomaly per 50.7 persons (1.97%). In no couple were chromosomal anomalies, including Yq11 microdeletions, found in both partners. The frequency of such aberrations among the two sexes appears to be similar, i.e. 42 cases out of 2078 men and 40 cases out of 2078 women, corresponding to one anomaly per 49.5 men (2.02%) and one anomaly per 51.9 women (1.92%) respectively. Therefore the prevalence of couples at risk to give rise to a genetically unbalanced zygote due to some constitutional chromosomal defect is 3.95%,

Table II. Karyotype findings among the male partners of the couples with history of gravidity ≥ 1 and parity = 0

Karyotypes		Frequencies (% of 923 men)		
Gonosome trisomies	47,XXY	1 (0.11)	1 (0.11)	18 (1.95)
Gonosomal mosaics	46,XY (90%)/46,X del(Y) (10%)	1 (0.11)	1 (0.11)	
Translocations	45,XY t(13;14)(p11;q11)	2 (0.22)	13 (1.41)	
	45,XY t(13;15) (p11;q11)	1 (0.11)		
	45,XY t(14;14)(p11;q11)	1 (0.11)		
	46,XY t(1;18)(p32;q23)	1 (0.11)		
	46,XY t(4;13)(q;q22)	1 (0.11)		
	46,XY t(3;7)(p27;p21)	1 (0.11)		
	46,XY t(3;16)(q25;p13)	1 (0.11)		
	46,XY t(3;12)(p13;q24)	1 (0.11)		
	46,XY t(10;11)(q24;q11)	1 (0.11)		
	46,XY t(2;5)(q13;q ter)	1 (0.11)		
	46,XY t(2;8)(p25;q13)	1 (0.11)		
	46,XY t(10;22)(q24;q11)	1 (0.11)		
Other	47,XY +mar	1 (0.11)	3 (0.32)	
	46,XY (40%)/47,XY +mar (60%)	1 (0.11)		
	46,XY (97%)/46,XY t(15;20) (3%)	1 (0.11)		

Table III. Karyotype findings among the male partners of the couples with history of gravidity = 0 and parity = 0

Karyotypes		Frequencies (% of 1155 men)		
Gonosome trisomies	47,XXY	5 (0.43)	5 (0.43)	24 (2.08)
Gonosomal mosaics	46,XY (89%)/47,XXY (5.5%)/46,XX (5.5%)	2 (0.17)	5 (0.43)	
	46,XY (90%)/47,XXY (10%)	1 (0.09)		
	46,XY (30%)/47,XXY (70%)	1 (0.09)		
	46,X del(Y)(q11) (50%)/45,X (50%)	1 (0.09)		
Translocations	45,XY t(14;21)(p11;q11)	1 (0.09)	12 (1.04)	
	45,XY t(13;14)(p11;q11)	5 (0.43)		
	45,XY t(13;15)(p11;q11)	1 (0.09)		
	46,XY t(1;12)(p26;p15)	1 (0.09)		
	46,XY t(1;5)(q43;q21)	1 (0.09)		
	46,XY t(2;10)(p21;p13)	1 (0.09)		
	46,XY t(6;10)(q26;q32)	1 (0.09)		
	46,XY der21 t(21;y)(p11;q11)	1 (0.09)		
Other	46,XY inv(Y)(p11;q11)	1 (0.09)	2 (0.17)	
	46,XY inv(12)(p11;q13)	1 (0.09)		

Table IV. Karyotype findings among the female partners of the couples with history of gravidity ≥1 and parity = 0

Karyotypes		No. of cases (% of 923 women)		
Gonosomal mosaics	46,XX (90%)/45,X (10%)	6 (0.65)	13 (1.41)	30 (3.25)
	46,XX (90%)/47,XXX (10%)	5 (0.54)		
	46,XX (90%)/45,X (6%)/47,XXX (4%)	2 (0.22)		
Translocations	45,XX t(13;14)(p11;q11)	3 (0.32)	15 (1.62)	
	45,XX t(13;13)(p11;q11)	1 (0.11)		
	46,XX t(2;18)(q36;q24)	2 (0.22)		
	46,XX t(3;12)(p13;q24)	1 (0.11)		
	46,XX t(8;19)(q13;q12)	1 (0.11)		
	46,XX t(3;9)(p14;p22)	1 (0.11)		
	46,XX t(3;4)(q27;q25)	1 (0.11)		
	46,XX t(2;4)(q13;p ter)	1 (0.11)		
	46,XX t(6;7)(p21;q36)	1 (0.11)		
	46,XX t(2;14)(p24;q32)	1 (0.11)		
	46,XX t(4;19)(q33;q13.1)	1 (0.11)		
	46,X −X +der(X) t(1;X)(q12;p11)	1 (0.11)		
Other	46,XX (80%)/47,XX +mar (20%)	1 (0.11)	2 (0.11)	
	47,XX +mar	1 (0.11)		

Table V. Karyotype findings among the female partners of the couples with history of gravidity = 0 and parity = 0

Karyotypes		No. of cases (% of 1155 women)		
Gonosomal mosaics	46,XX (90%)/45,X (10%)	4 (0.35)	4 (0.35)	10 (0.87)
Translocations	45,XX t(13;14)(p11;q11)	1 (0.09)	3 (0.26)	
	46,XX t(2;5)(q14;q35)	1 (0.09)		
	46,XX t(1;8)(q35;q24)	1 (0.09)		
Other	47,XX +mar	1 (0.09)	3 (0.26)	
	46,XX inv(2)(p11;q12)	1 (0.09)		
	46,XX dup(18)(p11;32)	1 (0.09)		

having 82 couples out of a total of 2078 with one partner with a karyotype change.

Observed numerical chromosome aberrations were complete 47,XXY karyotype in six cases, gonosomal mixoploidies in 23 cases and presence of a marker chromosome in five cases. The complete gonosomal aneuploidies were found only in the male group, namely the six cases of 47,XXY, which configures the Klinefelter syndrome. All these subjects were totally azoospermic and belonged to G0P0 couples, with the only exception of one subject, affected by a severe oligozoospermia (< 10 000 sperm cells/ml), whose wife reported a history of one early miscarriage. The gonosomal mosaics were found to have a 2-fold higher prevalence in women than in men, i.e. 0.82% of all the women in comparison to 0.29% of all the men ($P = 0.037$). Marker chromosomes were found in two males, and three females, and in two cases it was detected in mosaic. SKY analysis demonstrated that in two cases the marker derived from a chromosome 15, while in the remaining three it arose from chromosomes 3, 16 and 22 respectively. In all these cases SKY assay results were confirmed by further evaluation with FISH.

Chromosome abnormalities were related to the sperm count (Table VI); 17 anomalies were detected in 219 azoospermic or severe oligozoospermic men (7.76%); 10 in 295 mild oligozoospermic patients (3.39%), and 15 anomalies in 1559 normal men (0.96%). The prevalence of karyotype changes is significantly higher in groups with lower sperm cell count ($P = 0.000$). No chromosomal anomalies were detected in five patients with obstructive azoospermia.

Structural chromosome changes observed in the whole cohort were 28 autosomal reciprocal balanced translocations, 16 Robertsonian translocations, three inversions, and a single case of duplication. All these anomalies were observed in 100% of metaphases, excepting a single case of autosomal translocation that was found in mosaic. The prevalence of translocations in men and women was comparable (1.2 versus 0.87% respectively). Robertsonian translocations were detected in 11 (0.5%) men and five (0.24%) women. The remaining reciprocal translocations were observed as single cases, except for two identical t(2;18) in the female group.

Prevalence of karyotype changes among women with a different history of gravidity shows some significant differences. In the group of female partners the prevalence of chromosomal aberrations was significantly higher among the women with G ≥ 1P0 history in comparison to those with G0P0 history, i.e. 3.25% of the G ≥ 1P0 women compared to 0.87% of the G0P0 women ($P = 0.000$). In detail, the prevalence of translocations and gonosomal mosaics were both significantly greater among the G ≥ 1P0 women than among the G0P0 ones ($P = 0.002$ and $P = 0.015$ respectively). On the other hand, in the male group the prevalence of karyotype changes among the partners of either G ≥ 1P0 or G0P0 couples was not significantly different, i.e. 1.95% of men belonging to G ≥ 1P0 couples in comparison to 2.08% of the men of the G0P0 couples. Each type of chromosomal change was similarly prevalent in both groups, with the only exception of the 47,XXY aneuploidy and of the gonosomal

Table VI. Chromosome changes related to sperm cell count observed in 2078 male partners

Sperm cell count	Patients No. (%)[a]	Aberrations	No. of cases (%)[b]	
Obstructive azoospermia	5 (0.24)	–	–	
Severe oligospermia azoospermia ($0–5 \times 10^6$ cells/ml)	219 (10.5)	47,XXY	6 (2.74)	17 (7.7)
		46,XY (89%)/47,XXY (5.5%)/46,XX (5.5%)	2 (0.91)	
		46,XY (90%)/47,XXY (10%)	1 (0.46)	
		46,XY (30%)/47,XXY (70%)	1 (0.46)	
		46,X del(Y)(q11) (50%)/45,X (50%)	1 (0.46)	
		45,XY t(13;14)(p11;q11)	2 (0.91)	
		45,XY t(14;14)(p11;q11)	1 (0.46)	
		Reciprocal translocations	3 (2.1)	
Mild oligospermia ($5–20 \times 10^6$ cells/ml)	295 (14.2)	46,XY (90%)/46,X del(Y) (10%)	1 (0.34)	10 (3.4)
		45,XY t(13;14)(p11;q11)	2 (0.68)	
		45,XY t(13;15)(p11;q11)	2 (0.68)	
		Reciprocal translocations	5 (1.69)	
Normal sperm cell count ($>20 \times 10^6$ cells/ml)	1559 (75.24)	45,XY t(13;14)(p11;q11)	3 (0.19)	15 (0.96)
		45,XY t(14;21)(p11;q11)	1 (0.06)	
		Reciprocal translocations	7 (0.45)	
		46,XY inv(Y)(p11;q11)	1 (0.06)	
		46,XY inv(12)(p11;q13)	1 (0.06)	
		47,XY +mar	1 (0.06)	
		46,XY (40%)/47,XY +mar (60%)	1 (0.06)	

[a]Percentage of 2078 subjects.
[b]Percentage of each subgroup.

mosaics, which were both 5-fold more prevalent in the G0P0 men group than in the G ≥ 1P0 groups, although this difference was not significant.

In all, 202 out of 2078 male subjects (9.72%), all with normal karyotype and belonging to the G0P0 group, were also investigated for Yq11 microdeletions due to poor semen quality spanning from severe oligozoospermia to total azoospermia. Ten of these patients (4.95%) showed a Yq11 microdeletion, involving the AZFc locus in eight cases and both AZFb and AZFc loci in the remaining two cases (not shown).

Discussion

In this prevalence study, only infertile couples undergoing either IVF or ICSI were analysed. As is usual in several European infertility centres, both partners of each couple underwent karyotyping before entering assisted reproduction treatment. This practice is aimed at reducing the incidence of pregnancy losses or congenital anomalies owing to genetically unbalanced gametes originated by parents carrying some chromosomal rearrangement. Moreover in this study we chose to report all the chromosomal abnormalities which might have some clinical expression, including those whose role in the pathogenesis of infertility is not clear, in order to add another baseline to further studies approaching the same problem.

In our population of 4156 subjects (2078 couples), in which ≥50% of individuals had some factor of infertility requiring IVF or ICSI, we have found a 1.97% prevalence of karyotype anomalies (excluding Yq11 microdeletions), and each subject with a chromosomal change was coupled to a cytogenetically normal partner. This means that the risk for an assisted reproduction candidate couple to have one partner with a chromosomal anomaly in the present study appears to be of 3.95%. Moreover, several studies in which infertile subjects without obvious signs of genetic disease were investigated for chromosomal abnormalities have disclosed prevalence of anomalies ranging from 1.3 to 13.1% of all the individuals screened (Hens *et al.*, 1988; Lange *et al.*, 1993; Mau *et al.*, 1997; Scholtes *et al.*, 1998; van der Ven *et al.*, 1998; Meschede *et al.*, 1998; Peschka *et al.*, 1999; Schreurs *et al.*, 2000; Gekas *et al.*, 2001; Sonntag *et al.*, 2001). Such a variability among different series is likely to be related to a different composition of the populations examined, resulting from different criteria in selection of the patients. Severe male factor infertility and recurrent pregnancy losses are both conditions associated with high rates of constitutional chromosomal abnormalities (Tharapel *et al.*, 1985; Vincent *et al.*, 2002), therefore the number of subjects with a history of recurrent miscarriages or bad semen quality may reasonably influence the frequency of karyotype changes in large groups of infertile couples attending assisted reproduction treatment. The present study, and those reported above, show higher frequencies of anomalies in comparison to live-born children surveys, also considering that all the newborns were screened, including those showing overt phenotypes related to major chromosomal anomalies (Bratkowska *et al.*, 1985; Nielsen and Wohlert, 1991). In a 13-year incidence study, where 34 910 newborns were screened for karyotype aberrations, the frequencies of autosomal and gonosomal changes were 1:164 (0.6%), and 1:426 (0.23%) respectively, while the overall frequency of all types of aberration was of 1:118 (0.85%) (Nielsen and Wohlert, 1991). According to the available data, our results confirm the higher risk for infertile couples, in comparison with the general population, to be carriers of some constitutional chromosomal rearrangement which may require further investigation before or after

implantation, or might contraindicate ICSI or IVF at all. The evidence of an increased frequency of genetic conditions which may underlie the constitution of a zygote with imbalance in gene dosage further stresses the importance of genetic counselling for the couples attending assisted reproduction treatment. Balanced translocations may interfere with chromosome pairing or disjunction in meiosis, leading to the release of unbalanced gametes, thus such anomalies are considered in the gamut of mechanisms of infertility (Martin and Spriggs, 1995; Engel *et al.*, 1996). It is notable that in our sample the frequency of 13/14 translocations is ~2-fold greater than in the general population, i.e. 1:377 versus 1:743.2, while the overall frequency of the translocations between chromosomes of the D group seems to be even 5-fold greater than in the general population, i.e. 1:277 subjects (0.36%) in comparison to 1:1221 subjects (0.08%) (Nielsen and Rasmussen, 1976; Bratkowska *et al.*, 1985).

In our study the analysed population was subdivided into two groups: presence (G ≥ 1P0) or absence (G0P0) of spontaneous abortion in the medical history. In the group of male partners, chromosomal rearrangements were more frequently found in the G0P0 group, although their prevalence was not significantly greater in comparison to the G ≥ 1P0 group. According to Vincent *et al.* (2002), the frequency of chromosome abnormalities was found to be related to the spermiogram features, being higher in patients with oligo/azoospermia than in those with normal sperm cell count. It is noteworthy that the group of normozoospermic men in our sample showed a prevalence of karyotype changes (0.96%) similar to that found in the general population (0.85%) by Nielsen and Wohlert (1991). This suggests that there is no rationale to perform karyotype analysis in every single male entering assisted reproduction programmes. It would seem more appropriate to perform cytogenetic evaluation in presence of a sperm cell count $< 20 \times 10^6$ cells/ml.

In the male group, the Klinefelter syndrome was the most common chromosome aberration, since it was present in seven azoospermic and three severe oligozoospermic men. This study confirms 47,XXY karyotype as a relatively frequent cause of male infertility (Amory *et al.*, 2000). In the overall population the frequency of Klinefelter syndrome is quite variable between different studies, ranging from 1:3564 males (0.028%) to 1:576 men (0.173%) (Bratkowska *et al.*, 1985; Nielsen and Wohlert, 1991; Bojesen *et al.*, 2003). In the present study the prevalence was considerably higher than previously reported, since the karyotype 47,XXY was detected in 1:346 infertile men. Such a result could be explained on the basis of the selected population examined. The second common chromosome change was the Robertsonian translocation, which was detected in 11 patients affected by severe-to-mild oligozoospermia and normal sperm cell count, confirming that these chromosome rearrangements interfere with the meiotic process, causing a total or partial block of spermiogenesis. Probably, reciprocal translocations, inversions and duplications act with the same mechanism. The screening for microdeletions of the AZF loci performed on the 202 oligo/azoospermic with normal karyotype disclosed 10 cases of this anomaly (4.95%). The microdeletion of AZF loci in Yq11 represent a well-characterized cause of azoospermia and oligozoospermia (Foresta *et al.*, 2001). Different degrees of clinical expressions have been identified: (i) complete deletions of AZFa or AZFb, which are severe conditions associated with Sertoli cell-only syndrome (SCOS) and maturation arrest respectively; (ii) the partial deletion of AZFa or AZFb which are associated, along with the partial or complete deletions of AZFc region (the locus most frequently involved), with variable phenotypes ranging from hypospermatogenesis to SCOS (Krausz *et al.*, 2003; Vogt, 2004). Identification of such anomalies may be important in the therapeutic management of male infertility, as the complete AZFa and AZFb deletions are usually associated with difficult retrieval of testicular sperm, while the partial-to-complete AZFc deletions are associated with a continued regression over time of the germinal epithelium leading to the progressive worsening of oligozoospermia (Krausz *et al.*, 2003; Vogt, 2004). Subjects with microdeletions therefore have a reduced chance to father without assisted reproduction treatment, nevertheless they always transmit the abnormality to the male progeny (Stuppia *et al.*, 1996; Hargreave *et al.*, 1998; Fujisawa *et al.*, 2001; Foresta *et al.*, 2001; Gatta *et al.*, 2002; Komori *et al.*, 2002; Dada *et al.*, 2004).

In the group of female partners, chromosomal changes were observed mostly in the G ≥ 1P0 group, suggesting that chromosome changes rarely interfere with the meiotic process. The most frequent chromosomal abnormalities observed were a few patterns of gonosomal mosaics, that were ~4-fold more prevalent among the women with history of pregnancy loss. Low grade female gonosomal mixoploidies, i.e. <10% of cells carrying aneuploid number of gonosomes, are not seldom found in women aged >35 years (Guttenbach *et al.*, 1995; Sonntag *et al.*, 2001). These patterns of mild mosaics seem to have no influence on the female reproductive axis, and are thus believed to be a finding limited to somatic cells. The impact of mild sex chromosome mosaics on ICSI outcome is still controversial (Scholtes *et al.*, 1998; Sonntag *et al.*, 2001). The present data suggest that mosaicisms >8% are true mosaicisms with potential effects on the female reproductive axis. Interestingly, in comparison to the general population (0.85%) (Nielsen and Wohlert, 1991), the prevalence of anomalies among women of the G ≥ 1P0 group (3.25%) was found to be nearly 4-fold greater, but comparable in the case of the G0P0 group (0.87%). It must be noted, however, that prior to assisted reproduction treatment it is impossible to establish in which category a woman will be placed. This suggests that, differently from what may be indicated for male partners, cytogenetic screening should be performed in all the women requiring assisted reproduction treatment.

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