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An epidemiological and genetic study of facial clefting in France. I Epidemiology and frequency in relatives[1]

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SUMMARY The frequencies of cleft lip with or without cleft palate (CL(P)) and isolated cleft palate (CP) have been estimated in France to be 0·082% and 0·035%, respectively, after exclusion of malformation syndromes. A genetic and epidemiological study has been carried out on 468 patients with CL(P) and 163 with CP. The results are given in detail and some specific points are discussed: the apparently low incidence in France, the relationship between sex ratio and abortion rates, the maternal effects, and the possibility of an association between CL(P) and CP.

The genetics of cleft lip with or without cleft palate (CL(P)) and isolated cleft palate (CP) have been studied by many investigators in various regions and countries.[1–11] The mode of inheritance and the role of environmental factors are not yet entirely clear. It is generally accepted that CL(P) and CP are developmentally and genetically different.[12] These malformations may be part of genetic syndromes with Mendelian inheritance or syndromes with multiple malformations, the aetiologies of which are not clear, or syndromes resulting from chromosomal aberrations. After removal of these cases, which represent a small proportion of clefts, there remain the cases which can be explained, according to most authors, by multifactorial inheritance. However, Chung *et al*,[9] using complex segregation analysis, and Chung *et al*,[13] using segregation analysis under a mixed model, could not discriminate between single locus and polygenic inheritance. Melnick *et al*[14] proposed allelic restriction as an alternative biological explanation.

We present the results of an epidemiological and familial investigation of cleft cases in France. In a subsequent paper, we shall perform segregation analysis on nuclear families and use recurrence risks in familial cases to discriminate between modes of inheritance and to detect possible heterogeneity.

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Material

There were 126 087 births (including stillbirths) in various maternity hospitals in France, which provided information on stillbirths and malformation syndromes.

Familial and epidemiological information was collected for 646 probands (478 with CL(P) and 168 with CP) attending plastic surgery departments of three Paris Hospitals (Hôpital des Enfants-Malades, Hôpital Saint Vincent de Paul, Hôpital Saint Antoine). Cases of cleft associated with chromosomal aberrations, multiple malformations, or recognised syndromes were excluded from the study. Some cases came from Paris and the surrounding areas and some from other parts of France. Family information was obtained by interviews with the mother or father or both and rarely with another family member. This information included a complete pedigree extended to third degree relatives, occurrence of facial clefts or other conditions in members of the family, birth dates and places of parents and grandparents, parental consanguinity, possible problems during pregnancy, and maternal diseases. When other family cases were reported, a confirmation of the diagnosis was sought.

TABLE 1 *Frequency of clefts in the population*

	No of births	*All cases of clefts*				*Cases of clefts excluding syndromes*			
		CL(P)		*CP*		*CL(P)*		*CP*	
		No	*Frequency (%)*	*No*	*Frequency (%)*	*No*	*Frequency (%)*	*No*	*Frequency (%)*
All births	126 087	121	0·096	71	0·056	104	0·082	44	0·035
Livebirths only	124 356	107	0·086	62	0·050	102	0·082	44	0·035

TABLE 2 *Associated malformations in 478 CL(P) and 168 CP probands*

Malformation	*No of cases among*		*Frequency in population (%)*
	CL(P)	*CP*	
Central nervous system	3*	0	0·03
Face	4*	1	0·07
Extremities	3	1	0·23
Skeleton	1*	0	0·01
Congenital dislocation of the hip	2*	4*	0·04
Heart	4	0	0·36
Diaphragm	0	1*	0·004
Digestive system	2	0	0·09
Male genitals	2	0	0·62

*Frequency significantly higher than in the French population.

TABLE 3 *Composition of the series retained for the study*

		CL	*CL + P*	*CP*
Sporadic cases				
	Male	58	193	48
	Female	31	91	87
Familial cases				
	Male	18	42	15
	Female	12	23	13
Total		119	349	163

TABLE 4 *Side of CL and association with CP*

	Unilateral		*Bilateral*	*Total*
	Left	*Right*		
CL(P)	261	95	112	468
CL	107		12	119
CL + P	249		100	349

Information on other conditions in patients was obtained from medical records.

Results

POPULATION FREQUENCY (TABLE 1)

The frequency of all cases of CL(P) and CP, including stillbirths, was estimated as 0·96 and 0·56 per 1000, respectively. When syndromes and stillbirths were excluded, the frequency was estimated as 0·82 and 0·35 per 1000, respectively. The frequency of malformation syndromes is much higher in stillbirths than in livebirths: 6·9 (12/1731) and 0·04 (5/124 356) per 1000, respectively, for CL(P) and 5·2 (9/1731) and 0·14 (18/124 356) per 1000, respectively, for CP. When only livebirths are examined the exclusion of malformation syndromes results in a decrease in incidence from 0·86 to 0·82 per 1000 for CL(P), and from 0·50 to 0·35 for CP.

ASSOCIATED MALFORMATIONS

Among the 646 probands, 21 cases of CL(P) and seven cases of CP had another malformation which was diagnosed at birth. For some of these malformations (table 2) the frequency in the probands is significantly higher than in the French population.[15] Although the association of these malformations with CL(P) or CP did not suggest a specific syndrome, these 15 cases (ten CL(P) and five CP) were excluded from subsequent studies, in order to make the sample as homogeneous as possible. Table 3 gives the composition of the series which was finally used for the study. There were 468 cases of CL(P) from 458

TABLE 5 *Sex ratio among affected and unaffected children*

	No of affected in sibship	*Affected children*			*Unaffected children*		
		Male	*Female*	*% male*	*Male*	*Female*	*% male*
CL(P)	1	291	149	0·661	427	397	0·518
	2	23	9	0·719	17	22	0·436
	⩾3	4	3	0·571	4	5	0·444
	Total	318	161	0·664	448	424	0·514
CP	1	56	96	0·368	158	151	0·511
	2	6	6	0·500	8	10	0·444
	⩾3	2	1	0·667	1	5	0·167
	Total	64	103	0·398	167	166	0·502

families and 163 cases of CP from 159 families. The total number of families is 616 because one family had two probands, one with CL(P) and one with CP.

SIDE OF CL AND ASSOCIATION WITH CP (TABLE 4)

Of all CL(P) probands, 24% are bilaterally affected. In unilateral cases, the left side is affected nearly three times as frequently as the right side. In 75% of cases, cleft palate is associated with cleft lip. In bilateral cases, this association is still more frequent (89%).

SEX RATIO

As observed in Caucasian populations, CL(P) is twice as frequent in males as in females (proportion of males: 0·665). The same is observed when CL is associated with CP (0·673) and when it is not (0·639). CP is almost twice as frequent in females as in males (proportion of males: 0·387). Table 5 gives the proportion of males among affected and unaffected children according to the number of those affected in the sibship. Our results are similar to those obtained by Bear.[16]

In CL(P), the proportion of males among affected children does not vary significantly between sibships with one and two affected children ($\chi^2 = 1{\cdot}91$, 1 df, $0{\cdot}20>p>0{\cdot}10$), but it decreases significantly when three or more children are affected ($\chi^2 = 6{\cdot}59$, 1 df, $0{\cdot}02>p>0{\cdot}01$). Among unaffected sibs, the proportion of males does not vary with the number of affected in the sibship ($\chi^2 = 1{\cdot}18$, 2 df, $0{\cdot}90>p>0{\cdot}50$) and is similar to that in the general population.

In CP, the proportion of males seems to increase with the number of affected children in the sibship but the variation is not significant ($\chi^2 = 1{\cdot}57$, 1 df, $0{\cdot}30>p>0{\cdot}20$). If we pool our results with those of Bear,[16] the variation is still not significant ($\chi^2 = 1{\cdot}67$, 1 df, $0{\cdot}20>p>0{\cdot}10$). Among unaffected sibs, the proportion of males does not vary significantly with the number of affected children in the sibship ($\chi^2=1{\cdot}66$, 1 df, $0{\cdot}20>p>0{\cdot}10$), and is similar to that in the general population.

FREQUENCY OF STILLBIRTHS AND SPONTANEOUS ABORTIONS

The proportion of stillbirths and spontaneous abortions among the other pregnancies of the mother was estimated according to sibship size (table 6) and to the number of affected children in the sibship (table 7). Sibship size was defined as the number of livebirths (and not the number of pregnancies as defined by Bear[16]). The control group was taken from Briard *et al.*[15] The decrease in the proportion of abortions with the number of affected children observed by Bear[16] is also observed in our sample,

TABLE 6 *Frequency of stillbirths and spontaneous abortions according to sibship size*

Sibship size	No of sibships			No of pregnancies*			Stillbirths						Spontaneous abortions					
							No			%			No			%		
	CL(P)	CP	Controls	CL(P)	CP	Controls	CL(P)	CP	Controls	CL(P)	CP	Controls	CL(P)	CP	Controls	CL(P)	CP	Controls
1	117	35	213	10	3	18	1	0	2	10·0	0	11·1	9	3	16	90·0	100·0	88·9
2	120	49	102	147	52	118	5	0	1	3·4	0	0·8	22	3	15	15·0	5·8	12·7
3	92	32	53	201	70	117	5	4	1	2·5	5·7	0·9	12	2	10	6·0	2·9	8·5
4	51	17	26	165	55	86	1	0	1	0·6	0	1·2	11	4	7	6·7	7·3	8·1
5	31	7	15	137	29	64	4	0	1	2·9	0	1·6	9	1	3	6·6	3·4	4·7
6	15	6	6	82	30	31	2	0	0	2·4	0	0	5	0	1	6·1	0	3·2
⩾7	32	13	13	260	130	98	4	10†	0	1·5	7·7	0	13	2	1	5·0	1·5	1·0
Total	458	159	428	1002	369	532	22	14	6	2·2	3·8	1·1	81	15	53	8·1	4·1	10·0

*Excluding proband (or one of probands) and procured abortions.
†Nine of these stillbirths are from one mother.

TABLE 7 *Frequency of stillbirths and spontaneous abortions according to the number of affected children in sibship*

	No of affected in sibship	*No of sibships*	*No of pregnancies**	*Stillbirths*		*Spontaneous abortions*	
				No	*%*	*No*	*%*
CL(P)	1	439	928	20	2·2	78	8·4
	2	17	43	2	4·7	3	7·0
	⩾3	2	9	0	0	0	0
CP	1	152	337	14	4·2	15	4·5
	2	6	18	0	0	0	0
	⩾3	1	6	0	0	0	0

*Excluding affected children and procured abortions.

though it is not significant for CL(P) or for CP. A significant decrease in the proportion of abortions with sibship size is observed in CL(P) ($\chi^2 = 15{\cdot}78$, 5 df*, $0{\cdot}01>p>0{\cdot}001$) and in the control group ($\chi^2 = 12{\cdot}82$, 4 df, $0{\cdot}02>p>0{\cdot}01$).

PARENTAL AGE AND BIRTH ORDER (TABLE 8)

Birth order is significantly higher for CP and CL(P) patients than for controls[15] ($0{\cdot}05>p>0{\cdot}02$). The increase is marked only for familial cases and may be the result of observation bias: the probability that another child will be affected increases with sibship size. Parental ages are not increased, except paternal age in familial cases of CP, which is probably the result of the increase in birth order. Increased paternal ages were found by some authors, among them Fraser and Calnan[17] and Woolf,[18] but not in other studies.

BIRTHWEIGHT (TABLE 9)

In general, the mean birthweight is similar for cleft children and for controls,[19] except for female CP where it is significantly lower ($10^{-3}>p>10^{-4}$). So far there has been no explanation for this phenomenon, which has previously been observed by Lutz[20] and Fraser and Calnan.[17]

*After exclusion of sibships of size 1.

TABLE 8 *Mean parental age and birth order*

	Paternal age	*Maternal age*	*Birth order*
CL(P)			
Sporadic	29·3±0·3	26·2±0·3	2·27±0·09
Familial	29·8±0·7	26·5±0·5	2·64±0·18*
Total	29·4±0·3	26·2±0·3	2·35±0·08*
CP			
Sporadic	30·0±0·6	26·7±0·5	2·52±0·20
Familial	32·4±1·6*	29·4±1·6	3·44±0·64*
Total	30·3±0·6	27·1±0·5	2·66±0·19*
Controls	29·6±0·4	26·9±0·3	2·12±0·08

*Significantly higher than controls.

TABLE 9 *Mean birthweight*

	CL(P)	*CP*	*Controls*
Male	3302±28	3365±104	3334±5
Female	3141±44	3016± 54*	3220±5

*Significantly lower than controls

FREQUENCY OF MALFORMATIONS IN SIBSHIPS

The incidence of malformations at birth (excluding clefts) in sibships of children with CL(P) or CP is 1·4% and 0·9%, respectively, no different from the general population (1·86%).[15]

MATERNAL EFFECTS

Effects of maternal diseases such as epilepsy and diabetes, or events during pregnancy such as metrorrhagia, infectious diseases, drug ingestion, irradiation, etc, were studied. Comparison with a control group, collected in three Paris maternity hospitals (E Bois, personal communication), did not show any significant difference, except for epilepsy. Ten mothers of 11 probands were epileptic or had a positive history of convulsions. Five of them were treated, most of them only with phenobarbital (4/5) and one of them had two children with CL + P. Two mothers were not treated and the three others had convulsions but were not true epileptics. Thus, the frequency of epilepsy in mothers of probands is 1·7% (2·4% if mothers with a positive history of convulsions are included), which is significantly higher than in the control group (2·5 per 1000) ($p = 0{\cdot}037$ if only true epileptic mothers are considered). Among the 11 probands, five were familial cases: two of them were sibs and the three others had a more or less distant relative affected. It is interesting to note that two non-epileptic mothers received phenobarbital during pregnancy, a proportion which is not higher than in the control group (0·8%).

FREQUENCY OF CLEFTS IN RELATIVES

The proportion of relatives with clefts is given according to the degree of kinship (table 10), to the sex of the probands (table 11), to the relationship

TABLE 10 *Frequency of clefts in relatives according to degree of kinship*

	Relatives	*1st degree*			*2nd degree*			*3rd degree*
		Sibs	*Parents*	*Total*	*Uncles-aunts*	*Grandparents*	*Total*	*First cousins*
CL(P)	Affected	28	20	48	13	7	20	18
	Total	927	936	1863	3058	1872	4930	4858
	%	3·0	2·1	2·6	0·4	0·4	0·4	0·4
CP	Affected	10	9	19	8	3	11	6
	Total	350	326	676	1042	652	1694	1495
	%	2·9	2·8	2·8	0·8	0·5	0·6	0·4

TABLE 11 *Frequency of clefts in relatives according to sex of probands*

		Relatives	*1st degree*			*2nd degree*			*3rd degree*		
			M	*F*	*Total*	*M*	*F*	*Total*	*M*	*F*	*Total*
CL(P)	Male probands	Affected	18	14	32	7	6	13	7	4	11
		Total	608	603	1211	1607	1622	3229	1669	1606	3275
		%	3·0	2·3	2·6	0·4	0·4	0·4	0·4	0·2	0·3
	Female probands	Affected	9	7	16	4	3	7	4	3	7
		Total	334	318	652	881	820	1701	798	785	1583
		%	2·7	2·2	2·5	0·5	0·4	0·4	0·5	0·4	0·4
CP	Male probands	Affected	5	7	12	3	1	4	3	0	3
		Total	124	148	272	321	317	638	275	263	538
		%	4·0	4·7	4·4	0·9	0·3	0·6	1·1	0	0·6
	Female probands	Affected	4	3	7	4	3	7	2	1	3
		Total	211	193	404	537	519	1056	474	483	957
		%	1·9	1·6	1·7	0·7	0·6	0·7	0·4	0·2	0·3

TABLE 12 *Frequency of clefts in relatives according to the side (paternal or maternal)*

	Relatives		*1st degree (parents)*	*2nd degree*	*3rd degree*
CL(P)	Paternal	Affected	8	8	9
		Total	468	2410	2508
		%	1·7	0·3	0·4
	Maternal	Affected	12	12	9
		Total	468	2520	2350
		%	2·6	0·5	0·4
CP	Paternal	Affected	5	6	6
		Total	163	806	780
		%	3·1	0·7	0·8
	Maternal	Affected	4	5	6
		Total	163	888	827
		%	2·5	0·6	0·7

(paternal or maternal) of the relatives (table 12), and to the side of the defect and association with cleft palate for CL(P) patients (table 13). Only CL(P) relatives are counted as affected when the proband is CL(P) and similarly for CP. In general, the results are very similar to other studies. The following may be noted.

The frequency decreases sharply from first to second degree relatives, but remains the same for second and third degree relatives, particularly for CL(P).

There is absolutely no variation in the frequency of clefts in relatives according to the sex of the probands in CL(P). In CP, there is a significant increase in first degree relatives when the proband is a male ($0{\cdot}05>p>0{\cdot}02$) but not in other relatives.

There is no difference between paternal and maternal relatives of all degrees of kinship in CL(P) or CP, as observed by Bingle and Niswander.[21]

There is no significant variation in the frequency of CL(P) in relatives of CL(P) probands, according to the side of the defect and association with CP.

FREQUENCY OF ALTERNATE TYPE CLEFTING IN SIBS AND FIRST COUSINS

To test the existence of an association between the two types of clefts, the frequency of 'alternate type'* (AT) clefting in sibs and first cousins of the probands was compared with the frequency in French live newborns.

*CP when the proband was affected with CL(P) and vice versa, terminology which was proposed by Chabora and Horowitz.[22]

TABLE 13 *Frequency of CL(P) in relatives of CL(P) patients according to side of defect and association with CP*

		Relatives	*1st degree*	*2nd degree*	*3rd degree*
Association with CP	CL	Affected	13	6	4
		Total	440	1256	1139
		%	3·0	0·5	0·4
	CL + P	Affected	35	14	14
		Total	1423	3674	3719
		%	2·4	0·4	0·4
Side of defect	Unilateral	Affected	32	11	16
		Total	1419	3715	3697
		%	2·3	0·3	0·4
	Bilateral	Affected	16	9	2
		Total	444	1215	1161
		%	3·6	0·7	0·2

TABLE 14 *Comparison of frequency of AT clefting in sibs and first cousins of probands and frequency in the general population*

Proband	*Sibs*			*First cousins*			*Sibs + first cousins*		
	Total	*Affected*		*Total*	*Affected*		*Total*	*Affected*	
		*Expected**	*Observed*		*Expected**	*Observed*		*Expected**	*Observed*
CL(P)	927	0·324	1	4858	1·700	3	5785	2·024	4
CP	350	0·287	2†	1495	1·226	3	1845	1·513	5†
Total	1277	0·611	3†	6353	2·926	6	7630	3·537	9†

*If there is no association between CL(P) and CP.
†Significant (right tailed Poisson).

Sibs and first cousins were chosen because (1) they belong to the same generation as the proband, and thus represent a homogeneous population comparable to the general population for which the frequency has been estimated; (2) the diagnosis is easy to verify in most cases, especially in sibs; and (3) there are no problems of biased sampling resulting from the natural and social selection against people with CL ± P as would be the case among parents and grandparents.

Since the total number of sibs and first cousins is large and the expected frequencies of CL(P) and CP, if there is no association, is small, the expected numbers of AT sibs and first cousins follow a Poisson distribution.

The results are given in table 14. Among the 927 sibs of CL ± P probands, one has a cleft palate. If there is no association, the expected number is 0·324 (927 × 0·00035) which represents the parameter of the Poisson distribution. The probability that at least one has cleft palate is 0·277 (right tailed distribution), which is not significant. In first cousins, the observation of three CP among 4858 is not significantly greater than the 1·700 expected ($p = 0·243$). When both sibs and first cousins are added, the comparison is still not significant ($p = 0·146$). Among the 350 sibs of CP probands, two have CL(P), which is significantly greater than the 0·287 expected ($p = 0·034$). Among the 1495 first cousins, the observed number of three CL ±P is not significantly greater than the 1·226 expected ($p = 0·126$), but when sibs and first cousins are added the excess is clearly significant ($p = 0·019$).

When all the probands are pooled, the observed number of AT sibs is three, which is about five times greater than the expected number, 0·611 ($p = 0·024$). The observed number of AT first cousins is six which is about twice as many as the expected number, 2·926, but is not significant ($p = 0·077$). When sibs and first cousins are added, the observed number of nine AT clefts is clearly significant ($p = 0·011$).

Discussion

After this detailed description, we shall only discuss a few points of particular interest.

POPULATION FREQUENCY

The population incidences for CL(P) and CP may appear low in comparison with other European populations, among which the incidences are in general a little more than 0·001 for CL(P)[23] and around 0·005 for CP. This discrepancy cannot be solely the result of the exclusion of malformation syndromes, as seen in table 1.

Since our low frequency cannot result from missing diagnoses, especially for CL(P), we must

conclude that the frequency of clefts, particularly CL(P), is lower in France than in other European countries. The same discrepancy has been found for neural tube defects.[24]

SEX RATIO

The excess of males in CL(P) and of females in CP has been known for a long time. Under the multifactorial model, this would be the result of a shift between the distribution of liabilities of males and females.[25] In CL(P) the distribution of liability for males would be shifted to the right of that for females, resulting in a higher proportion of males. Niswander *et al*[26] reported a decrease in sex ratio in affected as well as in unaffected sibs as the number of affected subjects increased in families. They concluded that these observations were consistent with a two-threshold model: subjects whose liability exceeds the first threshold would be affected by CL(P) and those with liabilities exceeding the second threshold would be aborted early in development. As the number of affected children per sibship increases, there would be a greater shift in liability in males than in females. The result would be that relatively more male embryos are aborted, with consequent observed shifts in the sex ratio among affected as well as normal subjects. The same decrease in sex ratio was observed by Bear[16] but his conclusions were completely opposite to those of Niswander *et al.*[26] Observing a decrease in abortion rates with the number of affected subjects in sibships, he concluded that there was no argument in support of Niswander's model and that these results, combined with those of other investigators, indicated the existence of inherited factors reducing the abortion frequency in the sibships of CL(P) index cases. These reductions would apply only to female embryos, explaining the increase in sex ratio. However, our results suggest that the decrease in abortion rate with the number of affected subjects in sibships is very likely an observation bias. The abortion frequency decreases as sibship size increases, in cleft sibships as well as in control sibships. Since the number of affected subjects is positively correlated with sibship size, the reduction of abortion rate is very likely a consequence of this trivial correlation and not of a biological phenomenon. In fact, there is little need to postulate increased or decreased abortion frequencies to account for the reduction in sex ratio with the number of affected subjects in sibships. Whatever the mode of inheritance, the more affected subjects in a sibship, the more genetic factors are involved. If these genetic factors are not sex linked, the sex ratio in families with several affected sibs would be expected to be the same as in the general population.

MATERNAL EFFECTS

In reviewing the genetics of CL(P) and CP, Fraser[12] stated that up till then no maternal effect had been demonstrated. Bingle and Niswander,[21] studying the data from 16 investigators, compared the incidence of clefts in maternal and paternal half sibs and did not find any difference. They also compared the incidence in maternal and paternal first cousins and found the same figures. Similar results are obtained in our study.

The only positive maternal effect seems to be the increased frequency of epileptic mothers of CL(P) cases compared to the control group. Shapiro *et al*[27] found that epileptic mothers had a higher frequency of malformed children than non-epileptic mothers, with a relative risk of 1·6. Among these malformations, cleft anomalies were more common than in controls. Their data also suggested that epilepsy itself and not the anticonvulsant drugs was responsible for the increased risk, which is confirmed by our study. In particular, there was no association of the malformation with antenatal exposure to the drugs when they were taken for reasons unrelated to epilepsy.

FREQUENCY OF CLEFTS IN RELATIVES

The results are, on the whole, very similar to those obtained by other investigators. These results will be discussed fully in a subsequent paper on segregation analysis.

FREQUENCY OF ALTERNATE TYPE CLEFTING IN SIBS AND FIRST COUSINS

Our results tend to show an association between CL(P) and CP, which has been denied by most authors except Rank and Thomson[28] and Chabora and Horowitz.[22] However, these latter authors used pooled population data with differing incidences of clefting which obviously included malformation syndromes.

Although these syndromes have been excluded from our data, we cannot be sure that among families with both types of clefts there are not some cases of Van der Woude syndrome without lip pits in several affected members, as has been previously reported.[29] Moreover, the significant association is based on small numbers and needs a larger data base to prove this point. If this association exists, it means that there are certain common aetiological factors, genetic or environmental, responsible for each malformation, and not, as claimed by Chabora and Horowitz,[22] "that CL(P) and CP alleles are one and the same, or that they are at least closely linked".

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