Effect of Endogamy and Consanguinity on the Development of Labial Venous Malformations in Area of Tlemcen (West Algeria)

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Abstract: *Background*: Vascular malformation is extremely rare, yet has a profound impact on quality of life, aesthetic and functional disorders. *Aim*: To show that endogamy and consanguinity may represent risk factors for labial venous malformation (LVM) development. *Materials and Methodology*: Among the 18093 scrutinized families on a 20 years back period from marriage registers, five families with a child presenting LVM were recruited from two geographic areas, one highly endogamous (Nedroma), the other slightly endogamous (Maghnia). These families were recruited for a retrospective descriptive essay at the Pathology and Oral Surgery Department of Tlemcen University Hospital Center (north-west of Algeria). *Results*: Four cases of LVM were from the Nedroma region, the fifth one from the Maghnia region. High consanguinity level was registered in patient families from Nedroma. On the other hand, the blood group O frequency was slightly higher compared to that of the blood group non-O. *Conclusions*: The present study suggests that consanguinity could beget LVM and that endogamy could increase its prevalence. The postulated association between this genetic disease and the OO genotype seems to be not confirmed. Therefore, it would be interesting to seek the SNP markers in this region.

INTRODUCTION

Angioma is a recurring term used to designate some pathological abnormality, whether tumorous or malformative. The only common point between those two is the vascular system, which is affected in both cases (capillaries, veins, arteries, lymphatic vessels) [1]. It has become classical and convenient however to oppose vascular tumors (mostly cellular hemangioma) to vascular malformations [2]. Although rare, those malformations have been classified into four main types: capillaries, venous, lymphatic or otherwise artero-venous [3]. Vascular malformations in turn have been sub-classified as either venous or capillaro-venous, with infiltration that eventually becomes serious [4].

As for every other vascular malformation, venous malformations result from a vascular morphogenesis error [5]. While present at birth, those malformations progress slowly [6] and are generally detected either at adolescence or consequently to some traumatic circumstances. Facial forms may be localized in lips, eyelids or tongue [7,8], and are often responsible for aesthetic and functional disorders. Although what causes those malformations is still unknown, the malformations could be generated from some genetic factors [9-11]. Indeed, a mutation on chromosome 9p21 of a gene that

identifies substitution of a sole amino acid and causes ligand-independent activation of an endothelial cell specific receptor tyrosine kinase (TIE-2) domain was found. Moreover, existence of genotype heterogeneity among families with venous – cutaneomucous malformations was prominently displayed [3], leading to the conclusion that other factors and genes are involved. Hence, Brouillard and colleagues [12] recently highlighted a mutation of a – glomuline – gene for inherited cutaneous venous anomalies. This mutation would be involved in the development of glomuvenous malformations, even of multiple glomangiomatose familiar, which are not linked to 9p21, but instead link to a new locus on 1p21-p22, called VMGLOM (LOD score 12.70 with q 3D 0,00), bordered by AFMa205XD5 and D1S2775. However, their non-depressible and very painful characters on palpation, differentiate them to other types of venous malformations [13].

Due to their extremely rare occurrence, facially localized vascular malformations and notably those of venous or capillaro-venous type have so far shown considerable worldwide paucity in data and information, Algeria included. Considering the genetic factors implication in their appearance, the remarkably high level of consanguinity especially in north-west of Algeria [14,15], as well as the endogamy and consanguinity affects descendants (polymalformations, higher frequency association of pathogenic genes, rare and recessive diseases [16-18], we conjectured a potential involvement of endogamy and consanguinity in LVM development. Thus, a retrospective descriptive essay, including 18093 families among which five have a child with a LVM was accomplished at the Pathology and Oral surgery Department of Tlemcen University Hospital Center (north-west of Algeria). It is noteworthy that these families were selected from two separate geographic localities,

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one highly endogamous (Nedroma), the other slightly endogamous however (Maghnia).

MATERIALS AND METHODOLOGY

Subjects and Patients

From June 2005 to June 2007, 18093 families were scrutinized on a twenty years back period from marriage registers at the City Halls of Nedroma and Maghnia. The same letter was sent to all families, inviting those with a child presenting a labial malformation, for free consultation at the Pathology and Oral surgery Department of Tlemcen University Hospital Center (north-west of Algeria). Subsequently, five families having a child with LVM (Fig. **1**) were retained for the actual study. All parents of the patients are not affected.

Patient recruiting was done on a basis of clinical examination, identifying any labial malformation of blue depressible mass or under-mucous sheath, non-pounding and non-blowing yet increasing of volume when the patient is in an inclined position. The complementary histological examination carried out after chirurgy step showed thick and hyaline vessels with endarteritis and vascular thrombosis pictures, as well as bordered venous lakes with endothelial cells (Fig. **2**). Inclusion criteria consisted in geographic locality (Nedroma and Maghnia) and strictly labial localization of the malformation. Exclusion criteria consisted in artero-venous malformations. The study was carried out with Good Clinical Practice Guidelines and the Declaration of Helsinki, and was approved by the Scientific Council of Faculty of Medical Sciences, Tlemcen Abou-Bekr Belkaïd University. A questionnaire was distributed among all participants who in turn provided signed informed consent [19]. The mean age at the disease evolution peak was 12 ± 1 (range: 11-13 years).

Consanguinity Analysis and ABo Phenotyping Patients

Detailed three-generation pedigrees were drawn to analyze the consanguinity coefficient in the five recruited families. An analysis of the ABo group was made to identify the phenotype of all subjects and patients. ABo typing was performed using monoclonal antibodies (anti-A, anti-B and anti A+B) on whole blood samples collected in acid citrate dextrose (ACD)-contained tubes. Additionally, isogglutinin serum and erythrocyte tests were equally performed in order to unambiguously validate the serological test.

RESULTS

Four cases of LVM were recruited in Nedroma area and only one case from the Maghnia region. Results correspond to a prevalence of four cases/38000 inhabitants in Nedroma, and 1 case/70000 inhabitants prevalence in Maghnia. Moreover, malformation frequency as far as the studied families is of 8.14×10^{-4} (4/4912) and of 0.76×10^{-4} (1/13181) respectively to both regions. Therefore, risk of appearance for such pathology is almost 11 times higher in Nedroma than in Maghnia.

On the other hand, the highest consanguinity level was recorded in patient families of Nedroma region, with a mean consanguinity coefficient of 0.051. That of the Maghnia patient family was estimated to 0.016. Moreover, it should be stated that all patients from Nedroma were females (Table **1**).

Assessment of the frequency of ABo antigens and heterozygous and homozygous A, B, O alleles in patients with LVM and in their parents is resumed in Table **2**.

Fig. (1). Patients with labial venous malformations of the current study.
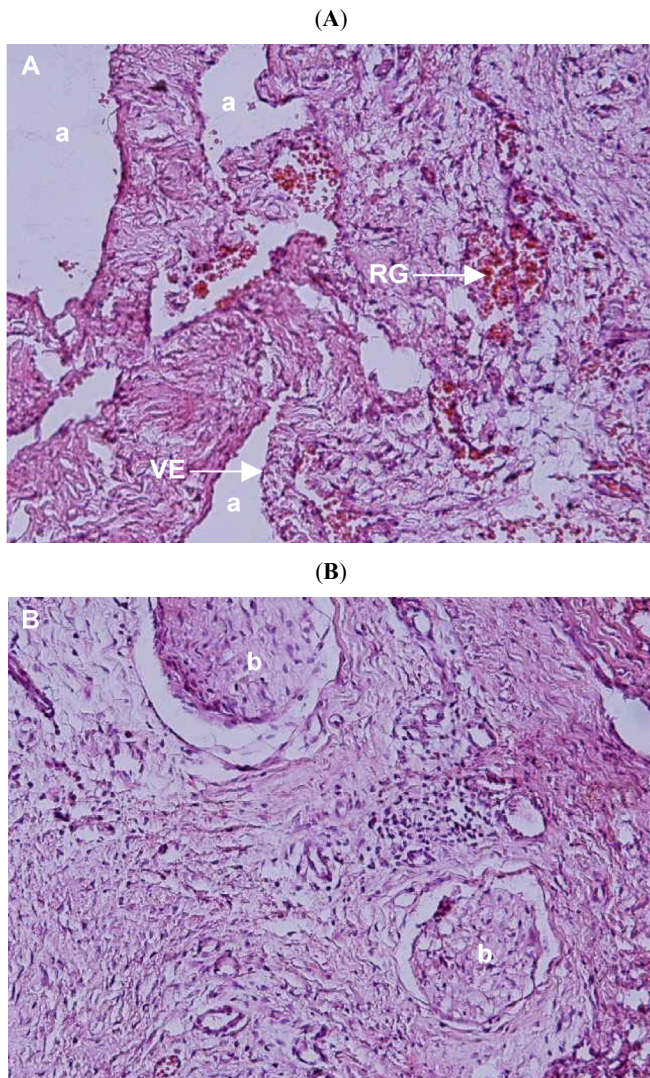
(A)

(B)

Fig. (2). Histological analysis of venous labial malformation. Postsurgical histological layers were stained with hematoxylin-eosin (H-E). (**A**) a: vascular cavity; RG: red globules; VE: vascular endothelium. (**B**) b: vascular thrombosis.

Table 1. **Prevalence of Labial Venous Malformation in Nedroma and Maghnia Regions (Tlemcen Area, North-West of Algeria)**

	Region	
	Nedroma	**Maghnia**
Number of inhabitants	38000	70000
Number of scrutinized families	4912	13181
Number of children with LVM	4	1
LVM frequency	8.14×10^{-4}	0.76×10^{-4}
Consanguinity degree of eligible families	5.1%	1.6%

LVM: labial venous malformation.

Unlike the Maghnia family, the frequency of homozygote alleles of the ABo system is higher than that of heterozygote alleles in the Nedroma area families (61.15% *vs* 38.85%). It is noteworthy on the other hand a weak increase in the frequency of the O alleles relatively to non-O alleles, *i.e.* all subjects: 16 (57.1%) *vs* 12 (42.9%); patients with LVM: 3 (60%) *vs* 2 (40%) respectively.

DISCUSSION

Spouse choice have direct consequences on the distribution, structure and heterogeneity of a population genetic heritage [20]. Preferential marriages limit freedom of choice, while retaining the heritage circulation within the clan [21]. From a sociologist viewpoint, individuals with similar characteristics have the tendency to wed together. This process of matrimonial choice is called homogamy [22]. It is known as endogamy when it is function of geographic locality. It could indeed depend on relationship, geographic isolation or social stratification [22-25]. Endogamy ascertains the power parents have on their kids, to a degree such as full participation in future spouse choice.

Most of the time, consanguinity weddings, *i.e.* with related subjects, are well-preferred within endogamous families. Such a practice is widespread in the Middle-East, North Africa and in South-West of Asia, representing higher than 50% of total marriages [26-30]. This matrimonial system seems well-maintained in the Arab world and in Maghreb countries [31].

A previous study in Algeria was performed in which a medical approach was used in order to seek unfavorable effects of consanguinity marriages on public health [32]. A more recent study described this type of union in urban and rural environments of Tlemcen area, considering the following criteria: structure (rate and type of relationship), social correlates, anthropological context and biological effects on the lineage [15]. Results showed that endogamy and consanguinity are more important in rural than in urban environment, where frequencies of marriages between related people represent 40.5% and 30.6% respectively. The importance of cultural context and educational level in spouse choice was particularly noticed in rural environment, with higher frequency than in urban environment of men with low educational level, especially in couples of related spouses.

Geneticists have classified consanguinity marriages according to consanguinity coefficient (f) [26,33]. High consanguinity levels result in losses of genetic variability, spoiled performances and increased risks of autosomal hereditary defect expression. In the present study, the clinical history of the studied patients families indicates a frequent consanguinity marriages notion among parents (f = 0.051 and 0.016 respectively for Nedroma and Maghnia regions). Consanguinity thus appears as a promoting factor for LVM appearance. Our study agree well with previous results obtained by Bénallègue and Kedji [32] who correlated significant consanguinity levels to polymalformation risk in Algeria. By comparison of the Nedroma region known for its high endogamy level with the Maghnia region, where population is a lot less endogamous, one may clearly notice the higher pathology prevalence in Nedroma than in Maghnia (4 cases/38000 inhabitants *vs* 1 case/70000 inhabitants). Moreover, Risk of appearance of such pathology is 11 times higher in Nedroma than in Maghnia, regarding the studied families. Our results thus suggest that endogamy may well increase LVM prevalence.

Table 2. **Blood ABo System Type and Homozygous and Heterozygous A, B, O Alleles Frequency in Patients with Labial Venous Malformation and in their Parents**

Eligible Family		Gender/Blood Type	Homozygous A, B, O Allele Frequency (%)	Heterozygous A, B, O Allele Frequency (%)
Nedroma Region			61.15	38.85
Family 1	Parents	Father: O (OO)/Mother: A (AO)	62.5	37.5
	Children	F/O (OO)* M/A (AO) F/A (AO) F/O (OO) F/O (OO) F/O (OO)		
Family 2	Parents	Father: B (BO)/Mother: O (OO)	57.1	42.9
	Children	F/B (BO) F/O (OO)* F/B (BO) F/O (OO) F/O (OO)		
Family 3	Parents	Father: O (OO)/Mother: O (OO)	100	0
	Children	F/O (OO)* M/O (OO)		
Family 4	Parents	Father: AB (AB)/Mother: O (OO)	25	75
	Children	M/B (BO) F/B (BO)*		
Maghnia region		-	40	60
Family 5	Parents	Father: (OO)/Mother: A (AO)	40	60
	Children	M/A (AO)* F/O (OO) M/A (AO)		

*Children with labial venous malformation. F: female. M: male. A, B, AB, O phenotype (genotype).

On the other hand, consequent to consanguinity is the increase of homozygote frequency and the decrease of the heterozygote one. The present study shows quite well the high homozygote alleles frequency, by comparison to that of heterozygote alleles in the Nedroma region, including patients with LVM (61.15% *vs* 38.85%). Thus, these results attest well of consanguinity in the studied sample. Yet, homozygocity is lower than heterozygocity in the patient family from Maghnia (40% *vs* 60%). Thus, one can note that children of the studied families from the Nedroma region are higher in consanguinity than those from the Maghnia region.

Despite the high O alleles frequency in children with malformation by comparison with non-O alleles (60% *vs* 40%), it seems difficult to associate these alleles to LVM, considering the reduced number of the studied sample. Therefore, it would be interesting to identify SNP (single nucleotide polymorphism) alleles within chromosome 9q, but also within chromosome 9p to confirm the implication of TIE-2 gene in the pathogenesis of these malformations in families of studied regions. Furthermore, previous studies done by Boon *et al.* [11] on three families generations with multiple venous, cutaneous and mucous malformations, suggested the implication of a 24cM locus on the short arm of

chromosome 9 (9p) in the malformation development risk, knowing however that genes of the ABo system are all localized on the long arm of the chromosome 9 (9q) [34,35]. Nevertheless, if our study requires measuring the Odds ratio (OR), O allele association with LVM would not be excluded (OR = 1.154). Such association remains nevertheless conjectural considering our non-representative sample, due to the extreme rarity of such pathology. Indeed, investigation showed a neat 1 case of vascular malformation per million inhabitants in the area of Paris, France (personal communication by Prof. Odile Enjolras, 2007).

CONCLUSIONS

In conclusion, a conducted study realized in two close geographic localities, yet far in levels of consanguinity/endogamy, lead to the conclusion that endogamy could increase LVM prevalence, and that consanguinity could beget its appearance. The postulated association between this pathology and the ABo system O alleles seems to be not confirmed.

Finally, functional labial disorders and especially esthetic prejudice of such malformations with facial localization as

well as the resulting difficulties in social contacts result often times in school failure, particularly during the adolescence.

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CONFLICT OF INTEREST

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