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Familial occurrence of classical and idiopathic trigeminal neuralgia

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ABSTRACT

Trigeminal neuralgia (TN) is a severe facial pain disease with unknown pathogenesis. It has been thought that the familial form of TN is rare with a prevalence of about 1–2% among affected individuals, but emerging evidence suggests a role of genetic factors. This study examined the occurrence of familial TN among patients with classical or idiopathic TN. Patients with TN recruited from a hospital registry received an informed consent form with a questionnaire, and individuals reporting other family members with TN underwent a structured phone-interview. For affected family members, type of TN, available clinical, imaging, management results and available hospital patient records were studied. Pedigrees for all affected families were established. This study included 268 patients with either classical or idiopathic TN. The familial form of TN was present in 41/268 (15.3%) patients, that is, 37/244 (15.2%) patients with classical TN and in 4/24 (16.7%) with idiopathic TN. Total 38 families were identified, with two affected members in 32/38 families (84.2%), three affected family members in 5/38 (13.2%) and four family members in 1/38 (2.6%) families. Comparing the 41 familial TN cases with the 227 sporadic TN patients showed significantly earlier onset of TN and a significantly higher occurrence of right-sided pain in familial cases, while there was no difference in gender distribution, occurrence of arterial hypertension or trigeminal branch involved. Among patients with classical or idiopathic TN, the occurrence of the familial form of the disease is more frequent than traditionally assumed.

1. Introduction

Trigeminal neuralgia (TN) or "tic doulourex" is a chronic neuropathic pain disorder characterized by spontaneous and elicited paroxysms of electric shock-like or stabbing pain, in the distribution of one or more branches of the trigeminal nerve [1]. Currently, vascular compression of the trigeminal nerve at the root entry zone is the most well-accepted cause of TN [2], and denoted *classical* TN. Microvascular decompression (MVD) is first line surgery for classical TN [1]. *Secondary* TN may result from lesions such as tumors or vascular malformations in the posterior fossa, or be caused by multiple sclerosis. When no cause is identified, TN is denoted *idiopathic*. Even though etiological factors have been identified, the underlying pathophysiology remains largely unknown. Understanding these mechanisms are required for better treatment strategies. Currently, a significant number of patients experience pain recurrence despite state of the art medical and surgical treatment, which extensively affect quality of life [3].

While genetic studies in TN have been scarce [4], several recent reviews point to a possibly important role of genetic factors in TN pathogenesis [5–7]. In particular, genes coding for voltage-gated ion channels such as sodium, calcium, potassium and chloride channels are important candidate genes in human studies [5].

Since long, it has been known that a familial form of TN exists [8–10]. A recent systematic review [5] referred to 27 families and 98 TN patients with familial TN reported in the literature between 1938 and 2019, and a prevalence of familial TN among patients with diagnosed TN about 1–2% [8,11–14]. These figures may represent underreporting as Di Steffano et al. [15] within a cohort of 88 TN patients identified familial TN in seven patients with classical TN and four patients with idiopathic TN. From whole-exome sequencing of eleven cases with familial TN, the authors reported variants in genes encoding voltage-gated ion channels and transient receptor potential (TRP) channels [15].

Genetic studies of familial TN could provide important insights about TN pathogenesis. To this end, the present study was undertaken to examine the occurrence of familial TN among patients with classical or idiopathic TN.

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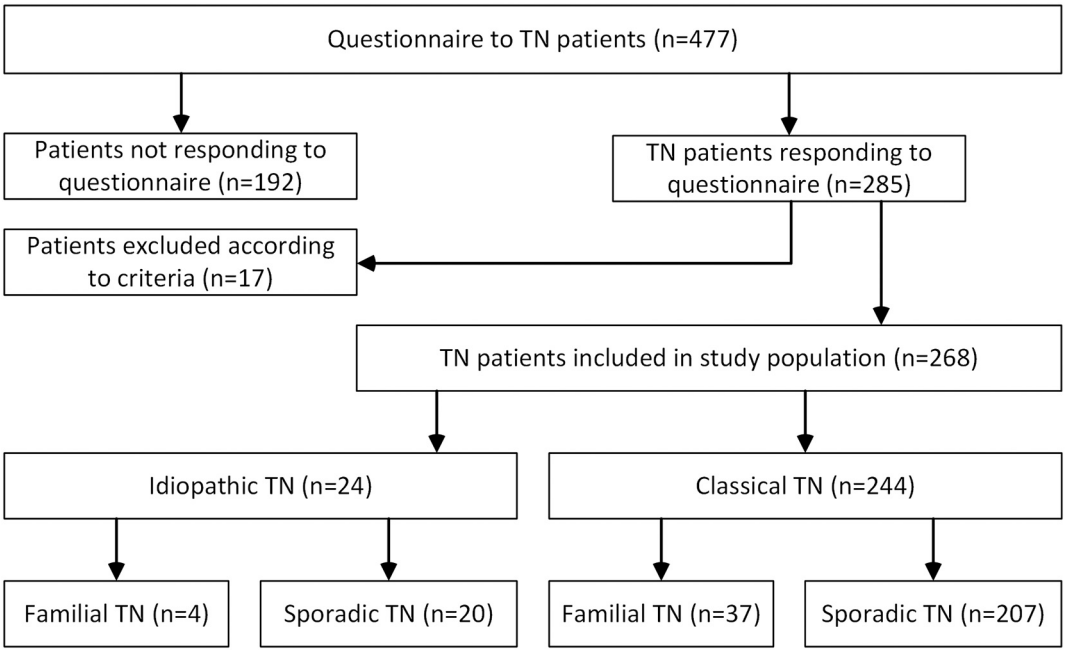

Fig. 1. Flow chart illustrating the selection process of defining the study population.

2. Methods

2.1. Study population

The study was approved by The Regional Committee for Medical and Health Research Ethics (REK) of Health Region South-East, Norway (2016/1656) and by Oslo University Hospital (2016/17151). It was conducted according to ethical standards according to the Helsinki Declaration of 1975 (and as revised in 1983). Patients were recruited from a quality registry at the Department of neurosurgery, Oslo university hospital-Rikshospitalet (Neurovascular-Cerebrospinal fluid quality registry; Re. 2011/6692) approved by the Institutional Review Board of Oslo university hospital. Participants were included after written and oral informed consent.

The information included in the quality registry were obtained as part of routine clinical work-up and treatment in the hospital, which is the only referral center for surgical treatment of trigeminal neuralgia in a population of about 3.1 million people.

Inclusion criteria were either diagnosed *"classical" TN"* or *"idiopathic TN"*, according to the classification by The international classification of headache disorders (ICHD-3), 3rd edition [16]. Magnetic resonance imaging (MRI) visualized neurovascular compression(s) in classical TN cases, whereas no abnormality was demonstrated on MRI in individuals with idiopathic TN. The classical and idiopathic TN types were further subdivided as *Type 1* when pain is characterized by short-lasting attacks (seconds to few minutes) of sharp, shooting, electrical shock-like pain, and as *Type 2* when the pain in addition had developed into a constant pain of aching, throbbing, or burning character [17].

Exclusion criteria were *secondary* TN, that is, TN secondary to e.g. multiple sclerosis or mass lesions in the posterior fossa (e.g. tumors or vascular malformations). Moreover, patients with so-called *"atypical"* trigeminal pain were excluded.

2.2. Study design and data collection

The aim was to identify which patients with diagnosed classical or idiopathic TN who had other family members with TN. The procedure was as follows: First, an informed consent form including a questionnaire about other family members with TN was sent to patients retrieved from the quality registry. The patients were asked to indicate in writing whether other family members had diagnosed TN. The individuals who consented to participate and who indicated other family members with TN underwent a structured interview by phone by the author (PKE). Every proband had been treated in the hospital and their patient records were studied to obtain information characteristics of TN, imaging results, and treatment results. The structured interview provided the following information: Contact information to other family members with TN, and available clinical, imaging and treatment data of the family members. Second, the other family members with TN were first contacted by the proband, and thereafter received an informed consent form with questionnaire. If willing to participate, they underwent an interview by phone. This structured interview gave information about type of TN, imaging and treatment data. Hospital patient records were studied when available. Third, family members with no TN were also interviewed after receiving an informed consent form.

Based on the information obtained from the questionnaires and phone interviews with affected family members, as well as non-affected family members, a pedigree of each affected family was drawn.

After receiving the informed consent form, also the hospital patient records of all participants with no other family members with TN were reviewed. From the clinical, imaging and management information, they were categorized as sporadic classical or idiopathic TN.

2.3. Statistical analysis

Comparisons of demographic and clinical information between the groups were performed by Pearson Chi-square test for categorical data and by independent samples *t*-test for continuous data. SPSS version 27 (IBM Corporation, Armonk, NY) was used for statistical analyses; accepting statistical significance at the 0.05 level (two-tailed).

3. Results

3.1. Patients

Fig. 1 illustrates the inclusion process. The questionnaire was sent to 477 TN patients, hundred and ninety-two patients did not respond, 17 individuals were excluded according to the exclusion criteria, leaving a

Table 1
Information about patients with sporadic or familiar trigeminal neuralgia (TN).

	Total	Sporadic TN	Familiar TN	Significance*
Demographic				
		227	41	
Total (N; %)	268	(84.7%)	(15.3%)	
Gender (F/M)				
	163	137	26	
F (N/%)	(60.8%)	(60.4%)	(63.4%)	ns
	105		15	
M (N/%)	(39.2%)	90 (39.6%)	(36.6%)	
Age at onset of TN	52.2 ±	52.9 ±	48.1 ±	
(yrs.)	12.9	12.5	14.6	$P = 0.03$
Co-morbidity				
Arterial	58			
hypertension	(21.6%)	49 (21.6%)	9 (22%)	
TN Diagnosis				
	244	207	37	
Classical	(91.0%)	(91.2%)	(90.2%)	
Type 1	244	207	37	
Type 2	68	58	10	
Idiopathic	24 (9.0%)	20 (8.8%)	4 (9.8%)	ns
Type 1	24	20	4	
Type 2	3	2	1	
Pain characteristics				
Side				
	168	140	28	
Right	(62.7%)	(61.7%)	(68.3%)	
	94		10	
Left	(35.1%)	84 (37.0%)	(24.4%)	$P = 0.025$
Bilateral	6 (2.2%)	3 (1.3)	3 (7.3%)	
Branch				
	62			
V1	(23.1%)	56 (24.7%)	6 (14.6%)	
	221	185	36	
V2	(82.5%)	(81.5%)	(87.8%)	ns
	161	136	25	
V3	(60.1%)	(59.9%)	(61.0%)	
Findings				
	244	207	37	
NVC	(91.0%)	(91.2%)	(90.2%)	
Treatment modality				
	222	191	31	
MVD	(82.8%)	(84.1%)	(75.6%)	
	27			
PRGR	(10.1%)	22 (9.7%)	5 (12.2%)	ns
PBC	7 (2.6%)	6 (2.6%)	1 (2.4%)	
Medications alone	23 (8.6%)	17 (7.5%)	6 (14.6)	

* Significant differences between sporadic and familiar TN were determined by independent samples t-test for continuous variables and by Pearson Chi-square test for categorical data.

study population of 268 patients. Forty-one of the 268 TN patients (15.3%) had other family members with TN, which included 38 families (Table 1). The family form was seen in 37/244 (15.2%) patients with classical TN, and in 4/24 (16.7%) with idiopathic TN (Fig. 1).

Table 1 compares the 227 individuals with sporadic TN and the 41 cases with familial TN. The familial cases experienced onset of TN at significantly younger age, and their pain was significantly more common on the right side. There were, however, no difference in gender distribution, occurrence of arterial hypertension, or involved trigeminal branches (V1, V2 or V3).

One or more neurovascular conflicts were in this material identified in about 9/10 patients both among the sporadic and familial forms. Moreover, surgical modalities were comparable between groups. Among the 41 patients with familial form, 31 underwent MVD, all with post-operative pain relief. It was, however, beyond the scope of this study to examine duration and degree of pain relief, or need for further medication.

3.2. Familial TN

The pedigrees of the 38 families with familial form of TN are presented in Supplementary Information (Supplementary figs. 1 to 38). The best fit mode of inheritance for the collection of families is autosomal dominant with incomplete penetrance. Most commonly, there were two affected family members (32/38 families; 84.2%), while three affected family members were seen in 5/38 families (13.2%) and four affected TN cases in 1/38 families (2.6%). Genograms of families with four or three TN cases are presented in Fig. 2. The inheritance of TN from parent to child was most common, with inheritance from mother to child ($n = 14$) more frequent than from father to child ($n = 8$). Fig. 3 presents examples of inheritance from parent to child. The female-to-male distribution of TN was about 3:2 (Table 1), which also is reflected in more frequent female inheritance (Table 2).

4. Discussion

The main observation of this study was occurrence of the familial form of TN in 41/268 individuals (15.3%) with classical or idiopathic TN. Familial form of TN in 37 of 244 patients (15.2%) with classical TN suggests that genetics factors are at play even though a neurovascular conflict is considered cause of TN.

Until recently, limited attention has been given to genetic factors in TN, reflect by the small number of genetic studies about TN [4]. Likewise, a recent systematic review identified in the literature from 1938 to 2019, 27 families with 98 TN individuals and a reported prevalence of familial TN about 1–2% [5]. In contrast to these previous figures, Di Stefano [15] recently referred to a material of 88 TN patients wherein seven patients with classical TN and four cases with idiopathic TN reported other familial members with TN. The present results of 41 probands and 38 TN families in a cohort of 268 TN cases represent the largest study so far and demonstrates that the familial form of classical and idiopathic TN is no rarity. Given an incidence of TN in the range 4 to 27/100000 people per year [18–20] and a female-to-male ratio about 3:2, an occurrence of familial forms of classical or idiopathic TN in about 15% of TN patients suggests a role of genetics in TN.

From the present genograms, the best-fit mode of inheritance is autosomal dominant with incomplete penetrance. The observations may therefore suggest that TN is multifactorial with instance of familial cases that look autosomal dominant with incomplete penetrance. Previous studies have suggested both autosomal dominant and autosomal recessive inheritance [8,13,14,21–29], autosomal dominant inheritance with variable penetrance [30], and also the phenomenon of genetic anticipation [12,25,31]. Several other factors need to be considered, such as late onset of symptoms about 50 years and incomplete penetrance.

The present results showed significantly younger age for pain onset in familial than sporadic cases of TN, which compares with previous findings [32]. In addition, the right side was significantly more affected than the left, which has also been reported before [15]. In contrast to this previous report, we found no higher occurrence in the second (V2) branch in familial cases.

The study excluded patients with secondary TN caused by space occupying lesions or multiple sclerosis, since these trigeminal pains are different from classical and idiopathic TN [33]. Possible genetic factors in these subgroups may be more complex. Moreover, due to the differences towards classical and idiopathic TN, the preferable surgical treatment for TN associated with multiple sclerosis is extensively debated [33], and trigeminal pain attributed to MS has a higher pain recurrence rate after surgery [34].

It may be of particular significance that familial TN is found in about 15% of individuals with classical TN, given that vascular compression of the trigeminal nerve is considered the cause of pain in these patients. Therefore, MVD is first-line surgery in classical TN [1]. Among the present 37 familial cases with classical TN, 31 underwent MVD and all had pain relief thereafter. It was, however, beyond the scope of this

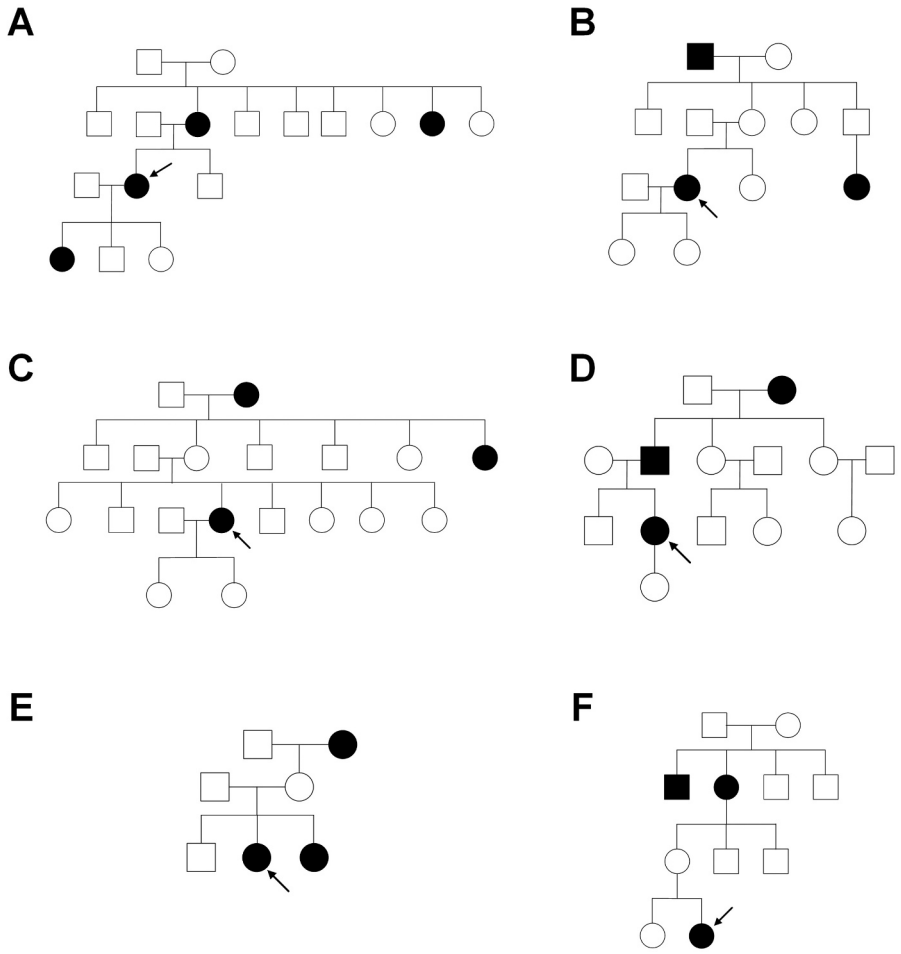

Fig. 2. Pedigrees of families with three or more affected family members. In one family (Family #19; A), four family members had the disease. Three members with diagnosed TN were found in another five families, i.e. Family #20 (B), Family #24 (C), Family #33 (D), Family #35 (E), and Family #37 (F). Among the remaining 32 affected families, two members were identified. Details about the individual families are given in Supplementary Material. Black symbols indicate individuals with diagnosed TN. Arrow indicates proband. Females: Circles. Males: Squares.

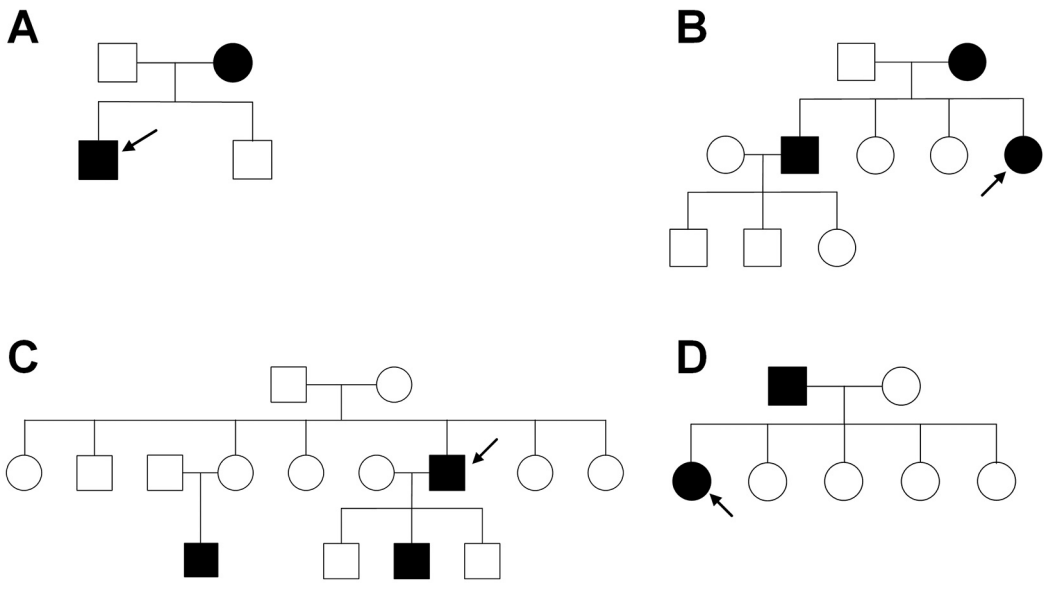

Fig. 3. The material discloses inheritance of TN from parent to child in 21 instances, more commonly from mother to child ($n = 13$) than from father to child ($n = 8$). The pedigrees provide examples of inheritance from mother to son (A; Family #18) that was seen in six cases, from mother to daughter (B; Family #32) that was seen in seven cases, from father to son (C; Family #1) that was seen in four cases, and from father to daughter (D; Family #29) that was seen in four cases. Details about the families are given in Supplementary Material. Black symbols indicate individuals with diagnosed TN. Arrow indicates proband. Females: Circles. Males: Squares.

Table 2
Gender distribution for different inheritance patterns.

Relative	Number	Percentage
Parent – Child (n = 22)		
Mother to Daughter/Son	13	62%
Father to Daughter/Son	8	38%
Grandparent – Grandchild (n = 13)		
Grandmother to grandchild	9	69%
Grandfather to grandchild	3	31%
Siblings (n = 7)		
Sisters	2	29%
Sister/Brother	4	57%
Brothers	1	14%
Nibbling's (n = 5)		
Female/Female	4	80%
Female/Male	1	20%
Male/Male	0	–
Cousins (n = 3)		
Female/Female	3	100%
Female/Male	0	–
Male/Male	0	–
Second cousins (n = 2)		
Female/Female	2	100%
Female/Male	0	–
Male/Male	0	–

Numbers refer to all observations of a given inheritance pattern.
Percentages are determined for each category.

study to determine degree and duration of pain relief, or compare pain relief in familial versus sporadic cases of TN. Our results of MVD in TN were previously reported [34,35]. Further studies should examine whether pain recurrence rate and response to medication differs between familial and sporadic cases.

It should be remembered that even though neurovascular conflicts are identified as causative of TN in classical TN, several aspects of the etiology behind TN remain unclear. For example, among 135 patients with unilateral classical TN, the presence of neurovascular contacts were seen on the symptomatic and asymptomatic side in 89 and 97%, respectively [36]. Moreover, the study reported evident neurovascular compressions on the symptomatic and asymptomatic sides in 53 versus 13%, respectively. These figures indicate that other factors than the neurovascular compression per se are at play in classical TN.

The pathophysiology behind TN is complex and incorporates both peripheral and central mechanisms. The peripheral mechanisms are best understood, with most attention given to the role of focal demyelination of the trigeminal nerve at the root entry zone nearby pons, which may render the primary afferent neurons hyper-excitable to mechanical pulsating compressions from blood vessels in the subarachnoid space [37]. Focus has particularly been given to the role of hyper-excitability of trigeminal ganglion neurons [38–40]. In this regard, the voltage-gated sodium channels are significant in regulating excitability of trigeminal ganglion neurons [41]. Neuronal hyperexcitability may as well develop in 2nd order neurons in trigeminal brainstem sensory nuclei and 3rd order neurons in thalamus projecting to the cortical grey matter, which may involve diminished gamma-aminobutyric acid- (GABA-) mediated inhibition [42]. At the cortical level, altered grey matter volume and connectivity have been implicated from neuroimaging studies in TN patients [6], though this may represent both consequence and adaption to chronic pain stimulation. Moreover, epigenetic factors may be at play in TN, e.g. via deoxyribonucleic acid (DNA) methylation that regulates gene expression. Bai et al. [43] found that peripheral inflammation altered DNA methylation in rat trigeminal ganglia, which was accompanied with abnormal expression of pro-nociceptive genes. The observation indicates that trigeminal ganglia pro-nociceptive genes may be subject to epigenetic modulation via DNA methylation.

Traditionally, arterial hypertension has been considered a risk factor for developing vascular compression of the trigeminal nerve leading to classical TN [12]. In the present cohort, the occurrence of arterial hypertension did not differ between cases with familial or sporadic TN. Moreover, in a previous study, we found no higher prevalence of arterial hypertension in patients with TN than the general population [44]. Therefore, to which degree arterial hypertension contributes to the impact of a neurovascular conflict in TN is unclear.

From the existing literature, there is an increasing number of possible candidate genes in TN [5–7]. In particular, mutation in genes coding for voltage-gated ion channels (sodium, calcium, potassium and chloride) and TRP channels may alter neuronal excitability that increase susceptibility for developing TN [15,42,45–47]. Siqueira et al. [46] reported altered expression of voltage-gated sodium channels $Na_V1.7$, $Na_V1.3$, and $Na_V1.8$ in TN cases compared with controls. Di Stefano et al. [15] performed whole-exome sequencing in 11 patients with familial TN and reported variants of several genes encoding voltage-gated ion (natrium, calcium, potassium, chloride) and TRP channels. Other candidate genes code for neuromodulators such as GABA and serotonin. Impaired GABA mediated inhibition was indicated by findings of damaging GABA receptor-binding gene-variants in TN cases [42]. Moreover, serotonin transporter gene-linked polymorphism differed between TN patients and controls, indicating a role of serotonin transporter in TN susceptibility [48]. Today's medical treatment of TN heavily relies on sodium and calcium channel blockers and GABA-modulating medications, including carbamazepine, gabapentin, lamotrigine and topiramate [6,49].

On this background, studies of mutations in ion channel genes may prove useful in family cases of TN. Hypothetically, neuronal hyperexcitability due to mutations in voltage-gated ion channels may render the trigeminal nerve more sensitive to neurovascular compression from blood vessels in the subarachnoid space.

Genetic testing was beyond the scope of this part of the study, but blood samples from participants of the study offer a novel opportunity for genetic studies.

Some limitations of the present study should be noted. It may be considered a limitation that the material constitutes merely 268 of the 477 TN patients since 192 patients did not respond. The occurrence of familial forms in these latter individuals remain unknown. On the other hand, a material of 268 patients with classical or idiopathic TN is the largest presented so far. Another possible limitation is selection bias since patients were recruited from a hospital registry dominated by TN patients from the neurosurgical population, mainly patients with classical TN. MVD is the prevalent type of surgery. This represents a bias as compared with TN in general. Another limitation is that in deceased family members, the exact diagnosis according to today's classification [16] cannot be made. On the other hand, the author considers the chance of erroneous diagnosis of TN in this cohort minor as the relatives were able to provide firm evidence for the TN diagnosis based on the patient history, including clinical presentation, treatment and hospital contacts.

5. Conclusions

The present findings of familial TN in about 15% of cases with classical or idiopathic TN differ from previous figures and demonstrate that the familial form of TN is no rarity. These results suggest a more important role of genetics in TN than traditionally considered. Understanding the genetic involvement in TN may open new doors for improved treatment of this debilitating pain disease.

Author contributions

Conceptualization and Design, P.K.E; Investigation, Formal Analysis and Visualization, P.K.E.; Supervision, Administration and Writing, P.K.E.

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Disclosures

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Appendix A. Supplementary data

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