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Dental care in hereditary angioedema : the French real-life experience of short-term prophylaxis and attacks

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Abstract

Background

In patients with hereditary angioedema (HAE), dental care and procedures are risk factors for angioedema attacks, which can sometimes be life-threatening. Short-term prophylaxis (STP), a procedure involving the administration of C1 inhibitor concentrate (pdC1inh), is therefore recommended to reduce the incidence of attacks.

Aims

To find out how the perception of HAE patients about their dental care is and to highlight the actual proportion of patients undergoing STP for at least one dental procedure in current practice and the obstacles to realize it, and finally, to describe angioedema attacks following dental procedures in French patients.

Methods

An online questionnaire completed by HAE patients was used to answer these questions. The questionnaire was distributed by the French national reference centre for angioedema (CREAK) and the French patient association (AMSAO) between January and December 2023.

Results

101 patients completed the questionnaire. 78.2% were patients with HAE-C1INH type 1 and 66 were women (65.3%) with a median age of 42 years (31.5–59.0). Only 65 patients (65.7%) informed their dentist about the presence of HAE. Forty-six patients (46.5%) reported feeling frightened before dental procedures, which resulted in 23 patients (24.0%) postponing their appointment. Finally, 49 out of 94 patients (52.1%) underwent dental treatment without STP because of a lack of knowledge (28.6%), because it was deemed unnecessary (14.3%) or because of organizational constraints (10.2%). Finally, 24 out of 99 patients (24.2%) said that they had experienced an attack of angioedema within 48 hours of a procedure, 40.9% of which was considered severe. We were not able to conclude about the efficacy of a STP to prevent an attack in our study ($p = 0.35$).

Conclusion

A number of obstacles, including fear, organisational problems and lack of knowledge, result in dental procedures being postponed and STP being performed in less than 50% of cases. Therapeutic education and multidisciplinary management should improve the preparation of patients with HAE.

Introduction

Hereditary angioedema (HAE) is a rare autosomal dominant disease. It is responsible for episodes of swelling which can be life-threatening due to asphyxia when the angioedema affects the upper airways, or following an occlusive syndrome when the episode is abdominal. The pathophysiological mechanism of HAE is in the majority of cases linked to an excessive production of bradykinin in association with a weight or functional deficit in C1 inhibitor (1). Some less frequent type of angioedema have normal C1 inhibitor with different pathophysiological mechanisms, particularly in relation to endothelial dysfunction (2).

Attacks can be treated with a bradykinin B2 receptor antagonist, icatibant, or with plasma derived C1 inhibitor concentrate (pdC1inh) (3, 4). The efficacy of these on-demand treatments has been clearly demonstrated, justifying their systematic use in cases of severe attacks in accordance with international recommendations (1). There is also the possibility of long-term treatment to prevent attacks. To date, pdC1inh and two anti-kallikreins, berotralstat and lanadelumab, are recommended and are available as first-line treatments in what is known as long-term prophylaxis (LTP) (1, 5, 6).

The key characteristic of angioedema attacks is that they are unpredictable. Nevertheless, triggers are frequently reported by patients, including stress, trauma and microtrauma (7, 8). In this respect, dental procedures such as dental avulsions and root canals are frequently reported triggers in the literature. A case of angioedema following dental impressions has even been reported (8, 9). Because of the proximity of the treatment area to the tongue and upper airways, dental treatment has sometimes been responsible for attacks with severe or fatal outcomes (10). However, some attacks can occur at a distance from the dental treatment area, such as in the abdominal area (9).

The potentially severe nature of attacks in this context justifies a short-term prophylaxis (STP) before any dental procedure. The STP currently recommended is intravenous injection of pdC1inh at a dose of 20 IU/kg within the six hours prior to the dental procedure. These recommendations are identical to those proposed for prophylaxis prior to surgery or caesarean delivery (1). Protection is not perfect, but it does reduce the incidence of attacks occurring after dental care or surgery. It does not eliminate the need for the patient to have and use if necessary the treatment for the attack (9). Furthermore, in the absence of any formal evidence suggesting that LTP also prevents post-dental care attacks, STP remains recommended in France, even if patients are treated with lanadelumab or berotralstat (1).

Nevertheless, there may still be a gap between recommendations and reality, particularly in relation to the organisational aspects of STP (need for an intravenous injection, finding a nurse) and coordination with the procedure. In addition, the effectiveness of attack treatment and, above all, of LTP may change patients' perception of the usefulness of STP in dental care.

In this study, we aimed to survey patients with HAE to evaluate the real-life effectiveness of STP prior to dental procedures, identify obstacles to its use, and explore patients' overall perceptions of dental care. The survey also examines the occurrence of angioedema following dental procedures and the contexts in which it arises. Our objective is to identify the limitations of STP, discuss strategies with patients to improve adherence, and enhance understanding of angioedema occurrence following dental procedures in the context of an increasing number of patients undergoing LTP.

Materials and methods

A prospective study, designed as an online questionnaire, was offered to adult patients diagnosed with HAE. The questionnaire included multiple items and collected retrospective data. The protocol was registered with the clinical research department of Grenoble Alpes University Hospital and received authorization, ensuring compliance with international guidelines and ethical standards for clinical research (CNIL).

Patient questionnaire

The questionnaire was distributed to HAE patients via the centres of competence and reference affiliated to the French national angioedema expert network (CREAK). The questionnaire was also distributed to patients via the French HAE patient association (AMSAO: Association des Malades Souffrant d'Angio-Oedèmes).

Patients had to have HAE, with or without C1inhibitor deficiency. This criterion, which defined the patients responding to the questionnaire, was based solely on the patient's declaration. Distribution of the questionnaire via the CREAK network or AMSAO alone limited the risk of participation by patients with mast cell angioedema or acquired bradykinin mediated angioedema.

The online questionnaire was made available to patients for completion from the whole year 2023. More than 90% of the questions were closed questions with single or multiple answers. The questions addressed their HAE pathology, their background treatment, their on-demand treatment and their knowledge of dental care in the context of HAE. It also addressed the question of their dental care, the use of STP, and the difficulties and apprehensions they had about carrying it out or not. Finally, patients were asked about attacks occurring in the 48 hours following dental treatment, in terms of the clinical presentation of the attacks, the dental treatment that triggered them, and the way in which they were treated.

Statistical analysis

Responses to the questionnaires were analysed using R software (v4.4.2; R Core Team 2024). The data is expressed in terms of the number of people associated with the percentage or the median with the interquartile range, depending on whether the data was qualitative or quantitative.

A univariate analysis was performed using non-parametric tests such as Fischer's exact test or Mann-Whitney-Wilcoxon test, depending on the type of variable. The tests were performed with an alpha risk of 0.05 on both sides. Thus, any p-value strictly less than 0.05 was considered statistically significant.

Results

Patients characteristics

From 1 January to 31 December 2024, 101 patients responded to the online questionnaire, including 66 women (65.3%) and 35 men (34.7%) with a median age of 42 years (31.5–59.0). The greatest proportion of patients had HAE with weight C1 inhibitor deficiency (HAE-C1INH-Type 1) in 78.2% of them, with functional C1 inhibitor deficiency in 5.9% and with normal C1 inhibitor in 8.9%. Finally, 7 patients (6.9%) were unaware of the specific type of angioedema they had.

Almost all patients had an on-demand treatment available, with 98 (97.0%) reporting this. For 89.8% of them, the available attack treatment was icatibant, and more than 79.6% knew how to self-administer the on-demand therapy.

Out of 100 patients for whom data were available, 61 patients (61%) had received or were receiving LTP. These were mainly treated with lanadelumab (68.8%), followed by berotalstat (11.5%), danatrol (11.5%), tranexamic acid (9.8%) and C1-inhibitor concentrate (3.3%). Of these 61 patients, 31 (55.4%) continued to have attacks, 9 of them at least monthly. Patients on LTP were older (median age 48 years vs 35 years; p = 0.023) and more often male (44.3% vs 17.9%; p = 0.009) than patients without LTP.

Patients and dental care

Of the 99 patients who answered the question, 43 (43.4%) visit their dentist once a year, 29 (29.3%) less than once a year and 27 (27.3%) more than once. Only 65 patients (65.7%) informed their dentist about their condition, while 34 (34.3%) did not, primarily due to forgetting (10/34; 29.4%) or fear of being refused care (4/34; 11.7%).

Forty-six patients (46.5%) reported feeling frightened before a dental procedure, with 17 patients (17.5%) citing this fear as the reason for not making an appointment or canceling an existing one. Additionally, fear led 23 patients (24.0%) to postpone their appointments. Organizational constraints were also noted, with 12 patients (12.4%) identifying this as a sufficient reason for not making or canceling an appointment, and 17 patients (17.7%) rescheduling their appointments for a later date.

The use of LTP was not associated with a reduction in fear of an attack related to dental care, nor did it influence perceived organizational constraints. Consequently, it had no significant effect on making, keeping, or canceling appointments ($p < 0.05$). However, the occurrence of angioedema following dental treatment was strongly associated with greater fear (83.3% vs. 34.7%; $p < 0.0001$) and a higher likelihood of postponing appointments (50% vs. 15.3%; $p = 0.0016$). Additionally, patients receiving LTP were more likely than those without LTP to recognize the need for STP when questioned (95.0% vs. 79.5%; $p = 0.0023$).

Finally, 49 patients out of 94 (52.1%) said they had undergone dental treatment without STP. When they did not take STP before dental care, it was primarily because 14 of them (28.6%) were unaware of the need for it in the specific case of their dental procedure. The other reasons are detailed in Table 1. This proportion of absence of STP was reported despite the fact that the vast majority of patients were aware that dental care is a trigger for an attack (97/100; 97.0%), that STP can reduce the risk (89/100; 89.0%) and that STP is recommended apart from a simple check-up visit to the dentist (91/98; 92.9%). Female patients used STP more often than males (55.6% vs 32.3%; $p = 0.0048$). Similarly, dental procedures such as dental avulsion were less often preceded by prophylaxis than all scaling, root canal and "simple care" procedures (28.0% vs 55.1%; $p = 0.034$). Furthermore, patients without STP were less likely to have informed their dentist of their underlying pathology (56.2% vs 77.8%; $p = 0.031$).

Table 1

Demographic characteristics of 101 patients surveyed and main outcomes about their dental care, their knowledge, the realization of short term prophylax difficulties regarding the short term prophylaxis before dental care and the percentage of angioedema attacks. (n = 101 patients, otherwise specified) *AE : a Long term prophylaxis, STP : Short term prophylaxis, STP+ : patients with STP at least once before a dental care, STP- : patient without ever STP before dental car with LTP while surveyed, LTP- : patients without LTP while surveyed, AE+: patients with at least one experience of angioedema attack during the 48 hours following : patients who have never experienced an angioedema attack during the 48 hours following a dental care.*

			Long term prophylaxis (LTP)					Short term Prophylaxis (STP)					Patients with angioedema attack after dental care			
	All patients *n = 101*		**Patients LTP +** *n = 61*		**Patients LTP-** *n = 39*		***P* value**	**Patients STP+** *n = 45*		**Patients STP-** *n = 49*		***P* value**	**Patients AE+** *n = 24*		**Patients AE-** *n = 75*	
Gender, n(%)	35	(34.7)	27	(44.3)	7	(17.9)	**0.009**	10	(22.2)	21	(42.9)	**0.048**	7	(29.2)	26	(3
-Male	66	(65.3)	34	(55.7)	32	(82.1)		35	(77.8)	28	(57.1)		17	(70.8)	49	(6
-Female																
Median age, year (IQR)	42.0	(31.5–59.0)	48.0	(34.5–59.0)	35.0	(25.5–54.5)	**0.023**	37.5	(29.7–51.7)	48	(33.0–61.0)	0.14	49	(39.5–66.0)	38.0	(3 5
Appointement with dentist, n(%) *n = 99*	29	(29.3)	20	(33.3)	9	(23.1)	0.43	13	(28.9)	12	(25.0)	0.90	7	(29:2)	21	(2
	43	(43.4)	26	(43.3)	17	(43.6)		21	(46.7)	22	(45.8)		8	(33.3)	35	(4
-Less than once a year	27	(27.3)	14	(23.3)	13	(33.3)		11	(24.4)	14	(29.2)		9	(37.5)	18	(2
-once a year																
-Twice a year or more																
Dentist's information, n(%) *n = 99*	65	(65.6)	39	(65.0)	26	(66.7)	1	35	(77.8)	27	(56.2)	**0.031**	18	(75.0)	47	(6
Dentist's reaction, n(%) *n = 65*	39	(60.0)	27	(69.2)	12	(46.2)	0.076	18	(51.4)	18	(66.7)	0.30	11	(61.1)	28	(5
	11	(16.9)	6	(15.3)	5	(19.2)	0.74	8	(22.9)	3	(11.1)	0.32	4	(22.2)	7	(1
-Information appreciated	6	(9.2)	3	(7.7)	3	(11.5)	0.68	3	(8.6)	3	(11.1)	1	2	(11.1)	4	(8
-Referral to another center																
-Refusal of care																
Reasons not to inform dentist, n(%) *n = 34*	4	(11.8)	3	(14.3)	1	(7.7)	1	2	(20.0)	2	(9.5)	0.58	2	(33.3)	2	(7
	10	(29.4)	5	(23.8)	5	(38.5)	0.45	3	(30.0)	7	(33.3)	1	1	(16.7)	9	(3
-Fear of refusal																
-Omission																
Knowledge about dental care and angioedema, n(%) *n = 100*	97	(97.0)	58	(96.7)	38	(97.4)	1	45	(100)	46	(93.9)	0.24	23	(95.8)	73	(9
	89	(89.0)	57	(95.0)	31	(79.5)	**0.023**	39	(86.7)	44	(89.8)	0.75	22	(91.7)	66	(8
	91	(92.9)	57	(96.6)	33	(86.8)	0.11	40	(93.0)	45	(91.8)	1	23	(95.8)	67	(9
-Dental care are a trigger of AE																
-STP can prevent AE																
-STP is necessary																
Fear before dental care, n(%) *n = 99*	46	(46.5)	26	(44.1)	20	(51.3)	0.54	23	(51.1)	20	(40.8)	0.41	20	(83.3)	26	(3

	Long term prophylaxis (LTP)							Short term Prophylaxis (STP)					Patients with angioedema attack after dental care			
	All patients *n = 101*		Patients LTP + *n = 61*		Patients LTP- *n = 39*		*P* value	Patients STP+ *n = 45*		Patients STP- *n = 49*		*P* value	Patients AE+ *n = 24*		Patients AE- *n = 75*	
Consequences of fear, n(%)	23	(24.0)	15	(25.4)	7	(22.2)	0.81	10	(22.7)	13	(27.7)	0.64	12	(50.0)	11	(1
-Delayed appointment *n = 96*	17	(17.5)	7	(16.9)	8	(18.9)	0.79	8	(17.8)	9	(19.1)	1	7	(29.2)	10	(1
- Appointment Cancellation *n = 97*																
Organizational difficulties, n(%) *n = 17*	4	(23.5)	2	(18.2)	2	(33.3)	0.58	2	(33.3)	2	(18.2)	0.58	2	(33.3)	2	(1
-Fear of organization	4	(23.5)	1	(9.1)	3	(50.0)	0.099	3	(50.0)	1	(9.1)	0.10	2	(33.3)	2	(1
-Lack of prescription	10	(58.8)	7	(63.6)	3	(50.0)	0.64	5	(83.3)	5	(45.5)	0.30	2	(33.3)	8	(7
-Difficulties to find a nurse	7	(41.2)	3	(27.3)	4	(66.7)	0.16	4	(66.7)	3	(27.3)	0.16	1	(16.7)	6	(5
-Coordination difficulties																
Consequence of organization difficulties, n(%)	17	(17.7)	11	(18.6)	6	(16.7)	1	6	(13.6)	11	(27.7)	0.29	6	(26.1)	11	(1
-Delayed appointment *n = 96*	12	(12.4)	7	(11.9)	5	(13.5)	1	7	(15.6)	5	(10.6)	0.55	5	(20.8)	7	(9
- Appointment Cancellation *n = 97*																
Realization of STP, n(%) *n = 94*	45	(47.9)	25	(43.9)	20	(55.5)	0.29	45	(100)	-	-	-	9	(39.1)	36	(5
Reasons not to realize STP, n(%) *n = 49*	14	(28.6)	8	(25.0)	5	(31.2)	0.74	-	-	14	(28.6)	-	4	(28.6)	10	(2
-Lack of knowledge	7	(14.3)	6	(18.7)	1	(6.2)	0.40	-	-	7	(14.3)		2	(14.3)	5	(1
-STP not necessary	4	(8.2)	2	(6.2)	2	(12.5)	0.59	-	-	4	(8.2)		2	(14.3)	2	(5
-Lack of time	5	(10.2)	3	(9.4)	2	(12.5)	1	-	-	5	(10.2)		2	(14.3)	3	(8
-Organization difficulties	2	(4.1)	0	(0)	2	(12.5)	0.11	-	-	2	(4.1)		1	(7.1)	1	(2
-Lack of prescription	2	(4.1)	1	(3.1)	1	(6.2)	1	-	-	2	(4.1)		0	(0)	2	(5
-Availability of product	1	(2.0)	1	(3.1)	0	(0)	1	-	-	1	(2.0)		1	(7.1)	0	(0
-Availability of nurse																
Angioedema attacks, n(%) *n = 99*	24	(24.2)	14	(23.7)	10	(25.6)	1	9	(20.0)	14	(28.6)	0.35	24	(100)	-	-

Table 1 summarizes the main reactions of dentists who are informed of the diagnosis, the reasons why dentists are not informed, patients' knowledge of drugs used for STP, the reasons why appointments are not made, cancelled or postponed, and the reasons given for not carrying out short-term prophylaxis.

Dental care and angioedema

Twenty-four patients (24.2%) reported having had an angioedema attack within 48 hours of dental treatment. The median time of onset was 4 hours (3–6) after dental treatment and the maximum 24 hours after treatment. They mainly followed dental avulsions (58.3%). These attacks were considered severe in 9 cases (40.9%), moderately severe in 11 cases (50.0%) and mild in 2 cases (9.1%). The location of angioedema when it was reported mainly concerned the face in 14 cases (58.3%), including 5 in the area where dental treatment was performed (20.8%), and 5 in the oropharyngeal or laryngeal area (20.8%). In 4 cases (16.7%), the location was abdominal. Of the 24 attacks, 17 (70.8%) were treated, including 10 (58.8%) with icatibant, 3 with pdC1inh (Berinert^{R}) (17.6%) and 4 (23.5%) with corticosteroids. Of the 9 patients who reported a severe attack, 3 (33.3%) were not treated, as were 2 out of 11 (18.2%) patients who reported a moderate attack and 2 out of 14 (14.3%) patients who presented with an attack localized to the face. Seven attacks (31.8%) required a visit to the emergency room. Of the 24 patients who experienced attacks, only 9 (39.1%) had received STP prior to dental treatment, including 5 (55.6%) with danazol, 2 (22.2%) with Berinert^{R} and 2 (22.2%) with tranexamic acid. Table 2 summarizes the characteristics of the attacks, the prophylactic attitude prior to treatment and their management.

Table 2

Characteristics of angioedema attacks in 24 HAE patients. (n = 24 patients, otherwise specified)

Type of dental care, n(%)	**Patients**	
-Dental avulsion	***n = 24***	
-Devitalization	**14**	**(58.3)**
-Tooth scaling	**4**	**(16.7)**
-"simple" dental care	**5**	**(20.8)**
	4	**(16.7)**
Median time between dental care and the onset of angioedema, hours (IQR)	4.0	(3.0–6.0)
Localization of attacks, n(%)	14	(58.3)
-Face	5	(20.8)
-Dental care area	1	(4.2)
-Tongue	5	(20.8)
-Oropharynx or Larynx	4	(16.7)
-Abdomen	2	(8.3)
-External genital organs	3	(12.5)
-Hands	2	(8.3)
-Feet		
Severity of the attacks, n(%) *n = 22*	2	(9.1)
-Mild	11	(50.0)
-Moderate	9	(40.9)
-Severe		
Treatment received, n(%)	7	(29.2)
-None	3	(12.5)
-pdC1inh	10	(41.7)
-Icatibant	4	(16.7)
-Corticosteroids		
Treatment received in Emergency Room, n(%) *n = 22*	7	(31.8)
Short term prophylaxis, n(%) *n = 23*	9	(39.1)
Short term prophylaxis received, n(%) *n = 9*	2	(22.2)
- pdC1inh	2	(22.2)
-Tranexamic acid	5	(55.6)
-Danatrol	2	(22.2)
-Corticosteroids		
Long term prophylaxis, n(%)	14	(58.3)
Long term prophylaxis drugs, n(%) *n = 14*	8	(57.1)
-Lanadelumab	1	(7.1)
-Berotralstat	5	(35.7)
-Tranexamic acid	1	(7.1)
-Danatrol		

HAE : Hereditary angioedema; pdC1inh : plasma derived C1 Inhibitor concentrates (always Berinert in our study)

Of note, patients experiencing angioedema were older than those who had never experienced it (median age 49 vs 38; p = 0.016). Dental avulsion was more frequently associated with the onset of angioedema compared with other dental treatments (root canal, scaling, simple dental care (p < 0.0001). The absence of STP was not associated with a higher risk of angioedema (p = 0.35), nor was the existence of LTP taken during a period of one's life (p = 1). Finally, the absence of STP was not associated with more severe attacks when they did occur (p = 0.38).

Discussion

Despite French and international recommendations confirming the need for STP with pdC1Inh, 49 of the 94 patients who answered the question did not undergo STP before dental treatment, despite a 92.9% level of awareness of the need for it and an 89.0% level of awareness of its efficacy in preventing angioedema attacks. The discrepancy between patients' knowledge and the rate of use of STP reveals obstacles and barriers to its use, which we have attempted to explore in our study. In addition, our survey revealed that 24.2% of patients had experienced at least one episode of angioedema attack in the 48 hours following dental procedure, 40.9% of which were reported as severe by the patients, and 70.8% of which required specific treatment for the attack.

Quite unexpectedly, we did not observe in our study an association between STP and the occurrence of attacks. This result differs from the literature, which has clearly demonstrated that STP reduces the incidence of attacks after dental care without however completely eliminating this risk (9, 11–13). Current recommendations place pdC1Inh as the treatment of choice for this prophylaxis (1). Unfortunately, the questionnaire did not allow us to know which molecule was used in all our patients who had undergone STP. However, among those who had presented with angioedema, more than 78% had used either C1 inhibitor concentrate or danazol, including 22.2% who had used pdC1Inh concentrate. However, we cannot extrapolate this proportion to all patients who reported using STP. Surprisingly, some patients used systemic corticosteroids or tranexamic acid, although these treatments have never been shown to be effective in STP.

In addition to the recommended choice of the right drug, the preventive strategy requires prior therapeutic education of the patient. Patient education is a crucial aspect of management, particularly for prophylaxis. It includes identifying situations with a risk of attacks, such as dental care, and developing self-management skills, especially organizational abilities (14). Our study confirms a good level of knowledge, since almost all patients knew that dental care was a potential trigger for an attack, as confirmed in the literature(8), that STP could reduce the incidence of attacks (9) and that STP was therefore recommended in the context of dental procedures(1). Interestingly, there was a higher proportion of patients on LTP who admitted the role of prophylaxis in preventing attacks. This likely reflects the educational approach and adherence to recommendations, which emphasize the use of STP even when the patient is on LTP (1). When the LTP was introduced, the physician may have insisted on the need to maintain STP during high-risk procedures. To our knowledge, no study in the literature has formally demonstrated that LTP can eliminate the need for STP. However, the significant reduction in attacks regardless of triggering factors in studies of lanadelumab or berotralstat could suggest a preventive effect on attacks following dental procedure (15). It might be interesting to further assess the incidence of angioedema attacks between a group of patients on LTP alone and a group of patients on LTP with STP.

Despite a high level of knowledge, more than half of the patients underwent dental procedures without prior STP. This discrepancy likely reflects fear or organizational constraints, as explored in our study. In all cases, regardless of the underlying reason, some patients experienced postponement or delay of treatment (up to 24.0%) or outright cancellation or failure to make an appointment (up to 17.7%). These challenges were further evidenced by the fact that the dentist was informed of the patient's HAE in only 65.6% of cases, with 11.8% withholding this information due to fear of treatment refusal. Informing the dentist is an important prerequisite for implementing STP. In our study, failure to inform the dentist was associated with a significant lower rate of STP. Furthermore, in practice, our study shows that refusal of care by dentists remains fairly infrequent (9.2%) in our cohort of patients surveyed.

The main reasons for not undertaking prophylaxis were a lack of knowledge (28.6%) and the belief that prophylaxis was unnecessary for the specific dental procedure performed (14.3%). Regarding knowledge, this appears to contradict the reported level of awareness among patients in our cohort. One possible explanation is that the level of knowledge was overestimated in our study. Providing more frequent or repeated therapeutic education, particularly when dental care is anticipated, could help address this gap (14). Another hypothesis is that stress or the interference of other challenges, particularly organizational ones, may limit access to or application of this knowledge. Regarding the patient’s assertion that STP was unnecessary, this may reflect the absence of a clear definition of dental procedures at risk for triggering attacks, despite the general consensus that any invasive procedure involving a contact factor, such as scaling, carries a risk. The occurrence of attacks in 16.7% of cases linked to 'simple' dental care underscores the need to refine this definition. Alternatively, it may highlight the role of stress or anxiety—frequently cited by patients as a trigger for attacks in studies—though this factor is often multifactorial and complex (16)

Patients' fear of experiencing an attack following dental treatment should not be underestimated, with 46.5% of the 99 respondents confirming such fears. This fear was significantly more prevalent among patients who had previously experienced attacks after dental procedures ($p < 0.0001$) and was the fourth most common reason for avoiding dental procedure, as well as for canceling or postponing appointments. Reducing anxiety, stress, and fear before dental treatment is crucial, and approaches such as therapeutic education and consultations with psychologists can be effective. Psychological support for patients and their families should be prioritized to address their needs and improve their quality of life(17, 18). In order to reduce the stress and fear induced by dental treatment, one team has investigated the use of a virtual reality headset, with positive feedback from patients. (19). In general, postponing or cancelling a dental appointment may result in a lower frequency of dental consultations compared to patients without an AEH. This was confirmed in a study by Singh et al. (20)

The third reason why STP was not carried out was organizational difficulties, reported by 10.2% of patients, with problems relating to the coordination of care and the time required, but also, more rarely, a lack of prescription to buy the C1 inhibitor concentrate or difficulty in finding a nurse. This reflects a procedure that requires the participation of several parties, from prescription to administration. STP also has a time constraint, as the concentrate must be administered within the 6 hours before the dental procedure. The publication of articles reporting the successful implementation of STP probably reflects the importance and the challenge to organize it as well as its effectiveness (21, 22). The use of non-medical resources by advanced practice nurses or coordination programs could provide a solution for patients with organizational difficulties, although the impact of advanced practice nurses in the specific context of hereditary angioedema has never been studied. (18, 23)

Finally, our study showed that 24.2% of patients had experienced at least one attack during dental care. There was no association between STP and the development of angioedema attack. This is probably due to the fact that the number of responding patients may have been too small, or to the fact that the

question was not enough precise. Given the design of the questionnaire, patients were not able to indicate that they had had a dental procedure without an attack if they had also experienced an attack during a following dental procedure for instance. This fact does not call into question the proven efficacy of short-term prophylaxis demonstrated in the literature(9, 12) .

The dental treatments most likely to cause attacks were dental extractions, a trigger frequently found in the literature, even taking into account that this is one of the most frequent dental procedures(9, 24). Moreover, in our cohort, this dental procedure was statistically significantly associated with the lowest rate of prior prophylaxis administration.

As we anticipated it, and similar to other studies in the literature(9), the vast majority of angioedema were located on the face (58.3%) and more precisely in the treatment area (20.8%), which explains the 40.9% of attacks described as severe. However, attacks at distance, particularly abdominal attacks, did occur, possibly involving a stress factor in the initiation of the attack. In terms of severity, with moderate to severe attacks in over 90% of cases and a 31.8% emergency room stay, attacks can be severe and sometimes fatal, as reported in the literature(10). Fortunately, the majority of patients who deemed it necessary to treat their attack were able to do so using icatibant (41.7%) or C1inhibitor concentrate (12.5%) as recommended (1). However, it is noteworthy that 33.3% of patients who reported a severe attack did not receive treatment, highlighting the need to provide further education on the importance of treating any severe attack. Another hypothesis to explain this high figure is that the attack occurred before the diagnosis of HAE, meaning the patient did not have access to appropriate treatment at the time. In our questionnaire, the requirement for a prior diagnosis before dental treatment was not explicitly addressed. The use of corticosteroids in 4 patients is atypical and may reflect the treatment of mast cell-mediated angioedema in an HAE patient, although this is not the recommended approach (25), or on the contrary, a lack of knowledge of the right treatment.

Our study has its limitations. No proof of a diagnosis of HAE had to be provided in order to complete the questionnaire. However, its distribution through the French CREAK network and the French patient association limited the risk of a patient not suffering from HAE completing the questionnaire. The wide distribution through the CREAK network and the association guarantees a good sampling of French patients, even though there may be an inclusion bias, particularly as regards a higher rate of completion by patients who have presented angioedema during dental treatment, as they are more aware of the issue. Memory bias can also be a limitation of our study but is linked to this type of study.

Conclusion

Our study highlighted a good level of patient awareness of the need for and effectiveness of STP in reducing the incidence of attacks following dental procedures. Nonetheless, it revealed an implementation rate of STP of less than 50%, with an impression of a lack of knowledge and as well as organisational problems. The fear of dental procedure with the possible and unpredictable occurrence of angioedema attack is also a striking feature of our study. Patient education and the setting up of a care pathway involving, in particular, advanced practice nurses and psychologists to coordinate STP would help to increase the use of STP and remove barriers to dental care. In the context of dental care, it would be interesting to evaluate the implementation of a multidisciplinary patient support strategy upstream of dental care, either through the acquisition of self-competence or through direct intervention. Finally, although our study was unable to demonstrate a direct effect of LTP on the occurrence of angioedema attacks, an effect already demonstrated in the literature. It raises once again the question of the preventive effect of LTP in the context of dental care which, if demonstrated, could enable patients on LTP to have an attack. More studies are needed on this subject.

Abbreviations

HAE
Hereditary angioedema
STP
Short term prophylaxis
LTP
Long term prophylaxis
PdC1Inh
plasma derived C1Inhibitor concentrate
HAE-C1INH
Hereditary angioedema with C1Inh deficiency
AMSAO
French patient association
CNIL
Ethical standard for clinical research
CREAK
French national reference centre for angioedema
• Human Ethics, accordance statement and consent to Participate declarations
Unnecessary according to French national regulations:National Commission for Information Technology and Civil Liberties (CNIL)

Declarations

Consent for Publication:

• Not Applicable

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Author Contribution

All authors (AB, DL, DG, JB, CE, OC, AS, MA, IBG, OF,LB) review the manuscript AB, DL, DG, JB, CE, OC, AS, MA, IBG, OF,LB participated in the study and included their patients AB and LB wrote the main manuscript

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