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REVUE FRANÇAISE
D'**Allergologie**

Revue française d'allergologie xxx (2017) xxx–xxx

Critical review

One voice for anaphylaxis in France: The vision of the centre of reference in rare diseases

Une voix pour l'anaphylaxie en France : la vision du centre de référence en maladie rare

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Received 10 June 2017; accepted 18 June 2017

Abstract

In October 2016, the French Minister of Health launched a call for new Centers of Reference in Rare Diseases (CRRD). In order to support quality clinical practice, prevention and research for patients presenting severe anaphylaxis, together with 15 French public health institutions (Competence Centers in Rare Diseases–CCRD), we submitted a proposal named ANAFIL. French data suggest that fewer than 30,000 people are affected by severe anaphylaxis, with 9.2 per 100,000 person-years based on data from the University Hospital of Montpellier. Cumulative incidence is an inadequate measurement here, since the reaction is no longer active once the episode is resolved and one patient can present different episodes of anaphylactic reactions. Covering 7 of 12 administrative regions in France, all 16 centres making up the ANAFIL network are linked to academic activities, supported by medical and patient associations. Given that anaphylaxis is considered a public health issue by the global allergy community, the ANAFIL proposal provides a key window of opportunity for the construction of a solid academic French consortium that will redress implementation gaps in the field.

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Keywords: Anaphylaxis; Classification; Epidemiology; International Classification of Diseases; Morbidity; Rare disease; World Health Organization

Résumé

En octobre 2016, le ministère des Affaires sociales et de la Santé a lancé un appel à la création de nouveaux centres de références dans les maladies rares (CRRD). Afin de soutenir la pratique clinique de qualité, la prévention et la recherche pour les patients souffrant d'anaphylaxie sévère, avec 15 établissements publics français de santé (Centres de compétences dans les maladies rares – CCRD), nous avons soumis une proposition nommée ANAFIL. Les données françaises suggèrent que moins de 30 000 personnes sont affectées par une anaphylaxie sévère et, 9,2 par 100 000 années–personnes, selon les données de l'hôpital universitaire de Montpellier. L'incidence cumulative est une mesure inadéquate, car la réaction n'est plus active une fois que l'épisode est résolu et un patient peut présenter différents épisodes de réactions anaphylactiques dans sa vie. En couvrant 7 des 12 régions administratives en France, les 16 centres composant le réseau ANAFIL sont liés à des activités académiques, soutenues par des associations de patients et de médecins. Étant donné que l'anaphylaxie a été considérée comme un problème de santé publique par la communauté mondiale de l'allergie, la proposition ANAFIL offre une opportunité clé pour la construction d'un solide consortium français académique, qui soutiendra les lacunes dans la mise en œuvre dans le domaine.

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Mots clés : Anaphylaxie ; Classification ; Épidémiologie ; Classification Internationale des Maladies ; Morbidité ; Maladies rares ; Organisation mondiale de la santé

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<http://dx.doi.org/10.1016/j.reval.2017.06.004>

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Abbreviations

AFPRAL	French Association for Prevention of Allergic Diseases (Association française pour la prévention des allergies)
CCRD	Competence Centers in Rare Diseases (Centre de compétence maladies rares)
CRRD	Centers of References in Rare Diseases (Centre de référence maladies rares)
ICD	International Classification of Diseases
INSERM	French National Institution of Health and Medical Research
RAV	Allergo-Vigilance Network (Réseau d'allergo-vigilance)
SFA	Société française d'allergologie
WHO	World Health Organization

1. Anaphylaxis' definition and severity degree

Since the term “anaphylaxis” was first coined by Charles Richet and Paul Portier [1], it has rapidly spread all over the world and its clinical importance as an emergency condition is now well accepted. Anaphylaxis is currently recognized for clinical use by healthcare professionals as a serious, acute, generalized, allergic or hypersensitivity reaction that can be life threatening and even fatal [2]. International guidelines concur that anaphylaxis is a medical emergency and requires rapid recognition and intervention [3–7]. Immediate treatment with administration of epinephrine, the only first-line intervention addressed to the management of this condition, is recommended to prevent the progression of an anaphylactic episode.

Either immune-mediated or non-immune mediated, anaphylaxis as a condition occurs on a continuum and anaphylactic episodes can begin, but not always, with relatively minor symptoms before progressing, in an unpredictable manner, to a life-threatening condition. In an attempt to improve communication concerning the understanding of anaphylaxis and support better management, several grading scales have been proposed. Reaching a classification of anaphylaxis' severity universally accepted would be valuable to:

- facilitate the communication among health professionals;
- report outcome;
- evaluate treatment options.

Since the classification proposed by Ring and Messner in 1977 [8], several severity-grading scales have been proposed to try to cover these needs. Timely, the efforts made over the last 5 years to improve the classification of allergic and hypersensitivity conditions in the current World Health Organization's (WHO) International Classification of Diseases (ICD)-11 revision succeeded in implementing the visibility of anaphylaxis and its severity, which provides worldwide standard terminology, definitions and classification for this condition [9,10].

2. Is anaphylaxis a rare disease? Critical view of epidemiology data

The French Minister of Health and Social Affairs defines “rare disease” when it affects less than 1 in 2000 people [11]. The Orphanet, lead by the French National Institution of Health and Medical Research (INSERM) and the French Ministry of Health, is responsible for developing an inventory of rare diseases and a classification system which could serve as template to update International terminologies [12]. When the WHO launched the eleventh revision of the ICD, a rare diseases Topic Advisory Group was established. So far, 5400 rare diseases listed in the Orphanet database have an endorsed representation in the foundation layer of ICD-11 [13], but anaphylaxis is not yet into the list.

In contrast to the majority of allergic or hypersensitivity conditions, worldwide anaphylaxis epidemiological data remain sparse for broader accurate comparable morbidity statistics. Recent publications have estimated the total annual incidence of anaphylaxis in Europe ranging from 1.5 to 7.9 per 100,000 subjects [14], and increasing incidence to 42/100,000 in the US [15]. However, the lack of standard methods and the wrong inclusion of cumulative incidence of anaphylactic episodes have been key negative issues in order to capture accurate and comparable anaphylaxis morbidity data. Cumulative incidence is an inadequate measure here, since the reaction is no longer active once the episode is resolved and one patient can present different episodes of anaphylactic reactions in his/her life. Most of the publications have so far considered the episodes (illness), regardless to the subject suffering of this condition (patient). Recent data demonstrated average rate of 0.32 (95% CI: 0.28–0.65) anaphylaxis cases per thousand populations per year [16]. In UK, the whole lifetime prevalence of anaphylaxis diagnosis is 50/100,000, thus less than 1/2000 of the definition of a rare disease [17].

Anaphylaxis epidemiological publications are also hampered by the inclusion of all severity degrees of anaphylaxis. Mild reactions in which manifestations are generally limited to one organ or system, such as the skin, usually do not incur any risk of death. The inclusion of these cases in the epidemiological studies provides mistaken perception of high and increasing incidence of severe anaphylaxis. Our focus is addressed to severe reactions in which the risk of mortality is strong and requires additional prevention measures and a coordinated management such as the one provided by the rare disease network in our country. To date, there is no available data regarding severe cases of anaphylaxis in Europe. French data suggests that less than 30,000 people are affected by severe anaphylaxis and, 9.2 per 100,000 person-years based on the University Hospital of Montpellier data [16].

3. The ANAFIL proposal: French network for a better management and prevention of severe anaphylaxis

The French Ministry of Health, in coordination with the State Secretariat for Higher Education and Research, implements a proactive policy based on the mobilization of health/research

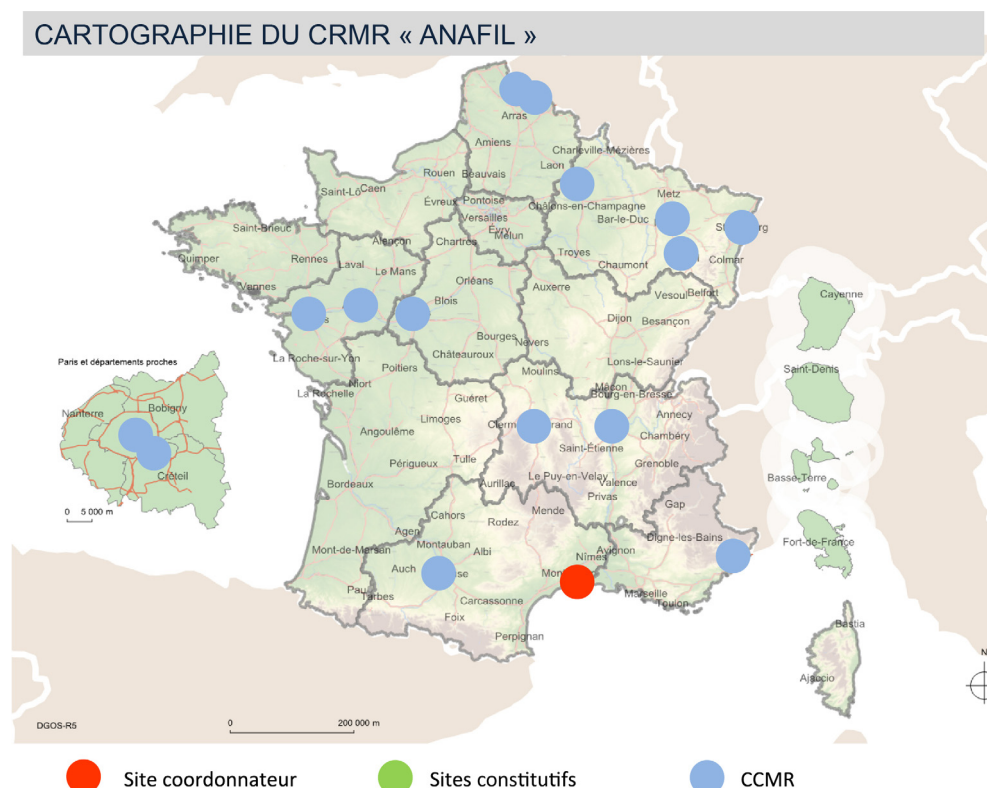


Fig. 1. Cartography of Centre of Reference in Rare Diseases (CRMR) and Competence Centers in Rare Diseases (CCRD) for the ANAFIL proposal for severe anaphylaxis.

professionals and patients' associations in order to improve quality diagnosis, management and prevention of the 3 million patients affected in France [11]. In October 2016, the French Minister of Health launched a call for new Centers of References in Rare Diseases (CRRD). In order to support the quality clinical practice, prevention and research for patients suffering from severe anaphylaxis, together with 15 French public health institutions (Competence Centers in Rare Diseases–CCRD) (Fig. 1), we submitted a proposal named ANAFIL.

The establishment of severe anaphylaxis competence centers connected to the referral center and to other centers of competence of the cities spread over the French territory will improve the prospective management of patients suffering from it, morbidity and presumably mortality by implementing individual and collective prevention measures and will prompt research projects which will rapidly improve knowledge in this field. Additionally, the ANAFIL proposal also intends to support refined investigations of specific severe anaphylaxis cases, such as the idiopathic anaphylaxis. Known diagnosis of exclusion, a significant proportion (24–59%) of anaphylaxis cases have been classified as idiopathic, which carries a lot of stress to the patients, knowing that they might react again (and possibly lose their life) to some noxious environmental elements not yet identified. The implementation of our proposal would be an instrumental move for a deeper investigation and understanding of the severe cases of unknown cause, still called idiopathic and, therefore, opening new perspectives for better management and prevention.

4. Building block of the ANAFIL network: lessons and perspectives

Covering 7 of 12 administrative regions in France (Fig. 1), all 16 centres composing the ANAFIL network academic institutions are linked to academic activities. Most of the allergy divisions (87.5%) are affiliated to public university hospitals, operating under Paediatrics (44%), Pulmonology (31%) or Internal Medicine (25%) departments. During the building block of the ANAFIL network, both national patients' associations (AFPRAL–French Association for Prevention of Allergic Diseases and Asthma & Allergies) and the non-governmental national allergy society (SFA) and Allergo-vigilance network (RAV), have been contacted with full support. Timely, all the efforts are aligned to considerable national and international actions for the better representation and management of allergic and related conditions and the recognition of the Allergy specialty.

At the national level, representatives of the French Federation of Allergy, which includes French Medical/Academic/Unions/Patients associations, have indeed been moving efforts to accommodate Allergy as a full academic specialty in France. A positive feedback came in 2016 and academic changes are expected to be launched in 2017. This academic move will allow better formation of health professionals, impacting in the quality management of allergic patients. Besides, national guidelines have been built in order to strengthen awareness among health professionals.

At the international level, the ICD is the world standard diagnostic tool for epidemiology, health management and clinical purposes. This includes the analysis of the general health situation of population groups. In French public institutions, the large scale alignment of individual diagnostic and procedural health expenses are allocated based on the ICD codes, currently, the tenth edition of the ICD. Patients' medical data are routinely recorded and coded under the ICD in institutional databases, under the Medical Information Departments' coordination and obeying the national ethical statements. A recognized reason for under-notification or under-estimation of anaphylaxis is the difficulty of coding anaphylaxis under the WHO ICD system. Limited number of ICD-10 codes is considered valid for specific anaphylaxis morbidity [18] and mortality [19]. Therefore, the institutional severe anaphylaxis morbidity statistics required for the ANAFIL proposal have only been estimated. New perspectives are expected for the coming years after the adoption of the eleventh version of the ICD. The ongoing ICD-11 revision opened the possibility of increasing the visibility of anaphylaxis through the construction of the pioneer Allergic and hypersensitivity conditions section. The development of the "Anaphylaxis" sub-section involved strong academic input and extensive consultation and agreement from the relevant WHO expert working groups and the support of six international allergy academies named Joint Allergy Academies [16,18–28]. Having anaphylaxis well classified and coded under the ICD-11 means that the WHO recognizes it as a real condition, which deserves proper diagnosis, management and prevention.

Given that anaphylaxis has been considered a public health issue by the global allergy community, the ANAFIL proposal provided a key window of opportunity for the construction of a solid academic French consortium, which will support implementation gaps in the field.

Role of funding source

This research was conducted with support from AstraZeneca (AZ ESR-16-11927).

Author contributions

Luciana Kase Tanno and Pascal Demoly contributed to the construction of the document (designed the study, analyzed and interpreted the data and wrote the manuscript).

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgement

We are grateful to all colleagues, health professionals and ANAFIL network representatives with whom we have been carrying on fruitful discussions: Alain Didier, Antoine Deschildre, Antoine Magnan, Bruno Crestani, Catherine Neukirch, Christine Sauvage, Cyrille Hoarau, Dominique Sabouraud, Etienne Beaudouin, Frédéric Berard, Frédéric de Blay, Jean Luc Bourrain,

Jean-Luc Fauquert, Jean-Marie Renaudin, Jocelyne Just, Martine Drouet, Michel Mertes, Pascale Dumond, Thierry Bourrier.

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