Central compartment atopic disease

Review Article

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Abstract

Objectives: To systematize the existing scientific evidence in relation to the pathology "Atopic Disease of the Central Compartment" (CCAD).
Study Design – Systematic Bibliographic Review.
Material and Methods: Conducting a systematic literature review in the MEDLINE, Cochrane Central Register of Controlled Trials and Cumulative Index to Nursing and Allied Health Literature databases, based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) model, selecting papers published between January 2010 and December 2022.
Results: Of the 3114 studies initially found, a total of 13 articles were selected for full analysis. More than half of the articles (69.2%) were published from 2019 onwards. A total of 1780 patients with CRS were analyzed. Of these, the number of patients with CHD was 372 (20.9%), with a male:female ratio of 2.16. Allergic rhinitis (98.5%), asthma (25.2%) and smoking (8.2%) were identified as comorbidities.
Conclusions: CCAD represents a variant of CRS described for the first time in 2017. It is associated with exposure to inhalational allergens and with edematous and polypoid repercussions in the middle and superior turbinates, as well as in the postero-superior region of the nasal septum. The basis of management of this pathology is medical treatment of the allergy, complemented, if necessary, with endoscopic sinus surgery.

Keywords: Central Compartment Atopic Disease; Chronic Rhinosinusitis; Nasal Polyposis; Allergic Rhinitis; Allergy.

Introduction

In 2014, White et al. described an association between isolated alterations of the middle turbinate (polyps or polypoid edema) and atopy to inhaled allergens[1]. More recently, Hamizan et al. corroborated these findings in a larger series of patients, showing that isolated edema of the middle turbinate (diffuse or polypoid) is highly specific for the presence of inhalational allergy (positive predictive value [PPV] = 91.7 and 88.9% likelihood ratio [LR] + = 8.0 and 6.2)[2]. Brunner et al. later described that polypoid alterations of the middle turbinate is

a unique condition with clinical associations that distinguishes it from nasal polyposis (NP), being more associated with allergic rhinitis (AR) than chronic rhinosinusitis (CRS)[3]. The proposed explanation for these changes is the exposure of the middle turbinate, especially its anterior surface, to inhaled allergens through normal airflow. The studies by White et al.[1], Hamizan et al.[2], and Brunner et al.[3] highlight the association between inhalational allergy and isolated alterations of the middle turbinate. However, DelGaudio et al. observed an advanced manifestation of this atopic process that also involves other structures of the central compartment of the nasal cavity: the superior turbinates and the posterosuperior region of the nasal septum[4]. These polypoid alterations of the central compartment have endoscopic and imaging repercussions. Thus, in 2017, the authors proposed the term *"Central Compartment Atopic Disease" (*CCAD)[4]. In recent years, a growing number of publications have described this entity. It should be noted that CCAD is included in the classification of primary CRS in the 2020 European Position Paper on Rhinosinusitis and Nasal Polyps as one of the diagnostic options for diffuse (bilateral) CRS with T-Helper endotype 2[5]. The objective of this study was to summarize the existing scientific evidence on CCAD and add to the existing knowledge in the Portuguese medical literature.

Materials and Methods

A systematic literature review was conducted in the MEDLINE, Cochrane Central Register of Controlled Trials (CCRCT), and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases, based on the PRISMA (*Preferred Reporting Items for Systematic Reviews and Meta-Analyses*) model[6], by selecting studies published between January 2010 and December 2022.

Using descriptors extracted from the Medical Subject Headings (MeSH), the terms "Central Compartment Atopic Disease," "Chronic Rhinosinusitis AND Allergic Rhinitis," and "Polypoid Changes of the Middle Turbinate" were used for the search. The inclusion criteria were human studies published in English between 2010 and 2022 that addressed CCAD or the relationship between CRS and allergy. Letters to the editor and case studies were excluded. The following data were extracted from the selected articles: authors, year of publication, sample size, type of study, and main contributions to scientific evidence in CCAD.

Results

Study Selection

The search in the previously mentioned databases yielded a total of 3114 articles (Figure 1); after eliminating the duplicate articles, 2677 articles were analyzed. Of these, after reading the title and abstract and applying the inclusion and exclusion criteria, 39 articles were selected for full reading. Finally, after complete analysis, 13 studies were selected (six retrospective cohorts, four systematic reviews, and thre e prospective cohorts) (Table 1). More than half of the articles (69.2%) were published from 2019 onwards.

Demographic characteristics

A total of 1780 patients with CRS were analyzed in the 13 included studies (two of the articles do not report the total number of patients analyzed). The number of patients with CCAD was 372 (20.9%), with a male: female ratio of 2.16:1 (Table 1). The mean age of the patients with CCAD at diagnosis was 39.6 years. Among the six studies reporting CCAD and asthma as co-morbidities, this group accounted for 25.2% of the total patients. Patients with CCAD and AR accounted for 98.5%, and those with CCAD and smokers accounted for 8.2%.

Clinical Presentation

Patients with CCAD experience an early onset of the disease (before the age of 20 years) and have a history of systemic atopy, including symptoms of AR, allergic conjunctivitis, and atopic dermatitis[10]. Many also report a history of asthma in early childhood with triggers

Figure 1
Flowchart according to the PRISMA guidelines for the selection of studies for inclusion in the literature review. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; CCRCT, Cochrane Central Register of Controlled Trials; CINAHL, Cumulative Index to Nursing and Allied Health Literature.

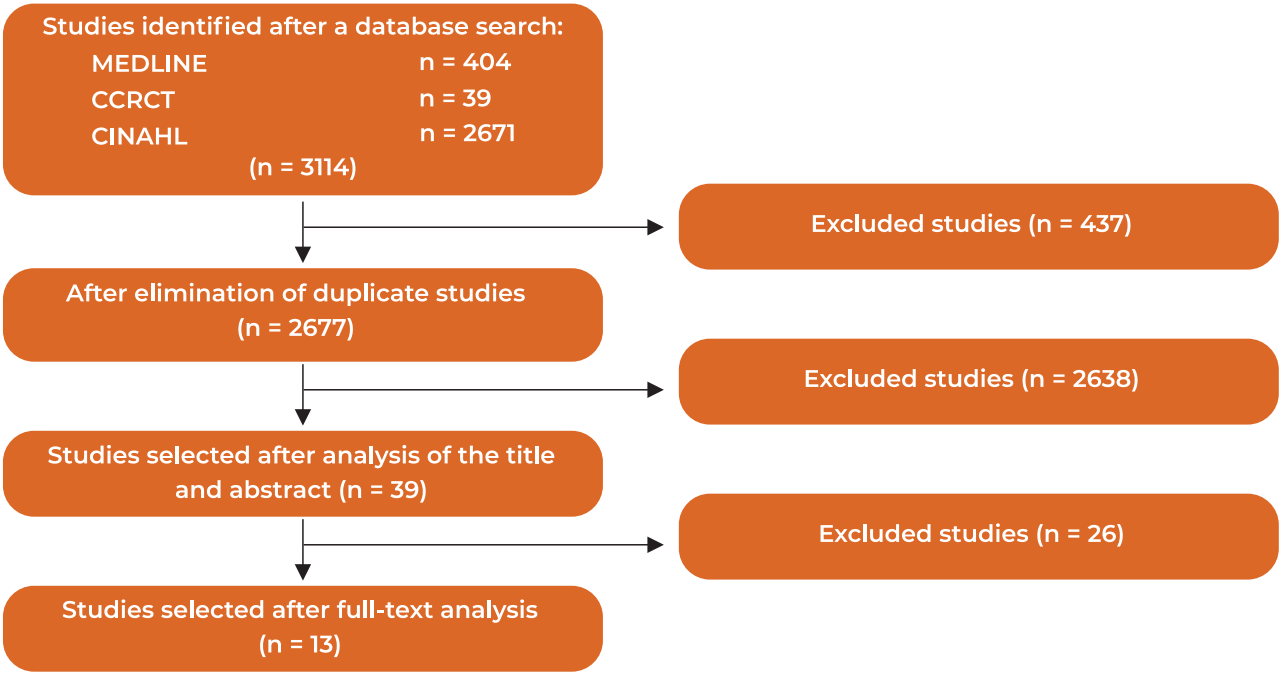


Table 1
Studies included in the literature review and data of the selected patient population

Authors	Year	Study Design	Total Number of Patients With CRS	Patients With CCAD (M/F)	Age of patients with CCAD, years (average and range)	Patients with CCAD and Asthma	Patients with CCAD and Allergic Rhinitis	Patients with CCAD and Smokers
DelGaudio et al.[4]	2017	Prospective Cohort	15	15 (8/7)	42.4 (23 – 71)	6 (40%)	15 (100%)	3 (20%)
Hamizan et al.[2]	2017	Prospective Cohort	187	106 (83/23)	36.3 (NR)	23 (21.9%)	106 (100%)	6 (5.3%)
Hamizan et al.[7]	2018	Prospective Cohort	112	63 (42/21)	44 (NR)	25 (40.3%)	63 (100%)	5 (8.3%)
Marcus et al.[8]	2018	Systematic Review	NR	NR	NR	NR	NR	NR
DelGaudio et al.[9]	2019	Prospective Cohort	72	59 (31/28)	49.4 (20-82)	NR	59 (100%)	NR
Grayson et al.[10]	2019	Systematic Review	NR	NR	NR	NR	NR	NR
Ho et al.[11]	2019	Prospective Cohort	446	NR	NR	NR	NR	NR
Marcus et al.[12]	2019	Systematic Review	NR	NR	NR	NR	NR	NR
Marcus et al.[13]	2020	Prospective Cohort	356	41 (24/17)	46.5 (NR)	7 (17.1%)	40 (97.6%)	NR
Helman et al.[14]	2020	Systematic Review	NR	NR	NR	NR	NR	NR
Roland et al.[15]	2020	Prospective Cohort	356	43	NR	NR	NR	NR
Lee et al.[16]	2022	Prospective Cohort	164	31 (27/4)	16.4 (NR)	5 (16.1%)	27 (87.1%)	NR
Kong et al.[17]	2022	Prospective Cohort	72	14 (10/4)	42 (NR)	2 (14.3%)	8 (57.1%)	2 (14.3%)

similar to those of other allergic symptoms. Local symptoms predominantly comprise nasal itching, sneezing, and watery rhinorrhea[11]. Often these patients do not have as many changes in olfaction as patients with CRS with Nasal Polyps (CRSwNP); they may report episodic sensations of pain or facial pressure. The reported symptoms typically respond to corticosteroid therapy. Regarding the intensity of nasal symptoms reported by patients, such as the persistence of rhinorrhea or frequency of sneezing, Halmizan et al. revealed that there were no significant differences between patients with CCAD and other patients with CRS[7]. In 2017, Brunner et al. demonstrated that patients with polypoid alterations of the middle turbinate were young, more likely to have AR, and less likely to develop asthma or aspirin-exacerbated respiratory disease (AERD)[3]. In 2020, Marcus et al. postulated that CCAD should be considered a clinically distinct entity from CRSwNP, with the former being associated with a significantly higher prevalence of AR and lower prevalence of asthma[13].

Histopathology

Elevated levels of total and serum specific IgE dominate CCAD. Although T helper 2 (TH2) cells are involved, these patients rarely have an elevated serum eosinophil count[10]. Some eosinophilic cells may appear in simple hematoxylin and eosin staining, but eosinophil aggregates or Charcot-Leyden crystals are rarely detected in mucin examination since these crystals are a characteristic of activated or degranulating eosinophils[10]. The histopathological alterations are only found in the mucosa derived from the ethmoid complex (superior and middle turbinates, as well as the posterosuperior region of the nasal septum). The mucosa of the inferior turbinate may be spared because of its distinct embryological origin[2].

Analytical Study

In patients with CCAD, both skin tests (skin prick test, intradermal skin test, and combined techniques) and serum IgE measurement for specific allergens are recommended. It should be noted that in some patients, although the measurement of systemic (serum) IgE may be negative, IgE is present locally in the nasal mucosa. This condition has been referred to as local AR or " "entopy[8]. Hamizan et al. compared nasal reactivity to allergens in the nasal challenge test with systemic reactivity defined by serum detection of specific IgE in patients with AR. The authors found local reactivity in 26.5% of patients previously considered non-allergic[2]. Persistent exposure to allergens and inflammation are considered necessary to produce the CCAD phenotype. Seasonal allergens are not usually the cause of this pathology, because chronic activation is required. Dust mites and other perennial allergens are more often associated with CCAD than pollens[10].

Endoscopic Study

Polypoid edema of the middle turbinate is considered a precursor or early stage of CCAD. Thus, at an early stage of the disease, only edema and/or polypoid alterations of the middle turbinate are found in endoscopy[4] (Figure 2). As edema progresses, it can negatively impact normal mucosal function, which allows allergens to act on neighboring structures, such as the superior turbinate and posterosuperior region of the nasal septum. Later, there may be an extension of the polypoid alterations to the unciform process and ostiomeatal complex[10]. Despite the extension of polypoid alterations to these structures, the ethmoidal, sphenoid, and maxillary mucosa are often almost normal.

Imaging Study

The most typical imaging alteration in CCAD is a thickening of the soft tissues of the central portion of the nasal cavity (upper and middle turbinates and posterosuperior region of the nasal septum), with preservation of the mucosa of the sinuses, especially their lateral walls (Figure 3). These changes were originally described as the "black halo" sign[15]. Roland et al. also reported that these patients have a low

Lund-Mackay score, and that opacification of the olfactory cleft is a late finding[15].

Secondary obstruction of the sinuses occurs when the central alterations begin to spread laterally to the sinus ostia or when the middle turbinates assume an oblique position, and not due to polypoid alterations of the sinuses themselves[10]. This post-obstructive nature of sinus involvement is demonstrated by the normal sinus mucosa found within these sinuses when they are surgically explored. These findings are reflected in the pattern of involvement in computed tomography (CT). Thus, in the early stages of CCAD, thickening of the soft tissues of the sinuses begins on the medial aspect of the ethmoid sinuses bilaterally. In contrast, in the most severe forms of the disease, almost complete opacification of the sinuses can be observed[4].

Differential Diagnosis

The pattern of nasal cavity mucosal involvement in the early stages of CCAD is clearly distinct from the other CRS phenotypes (with or

Figure 2
Nasal endoscopy images showing the typical findings of Chronic Rhinosinusitis with Central Compartment Atopic Disease: (A, B, and C) – evidence of polypoid edema of the middle turbinate and posterosuperior region of the nasal septum

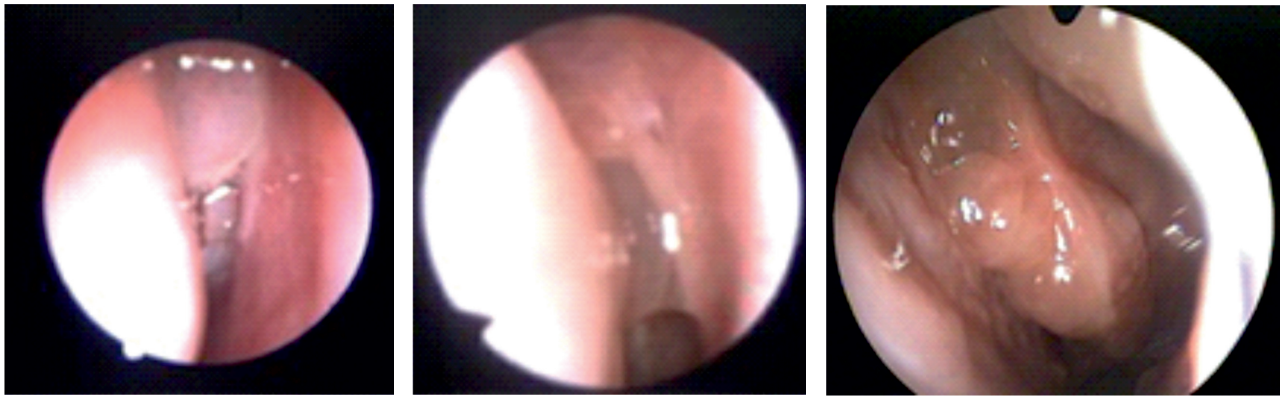
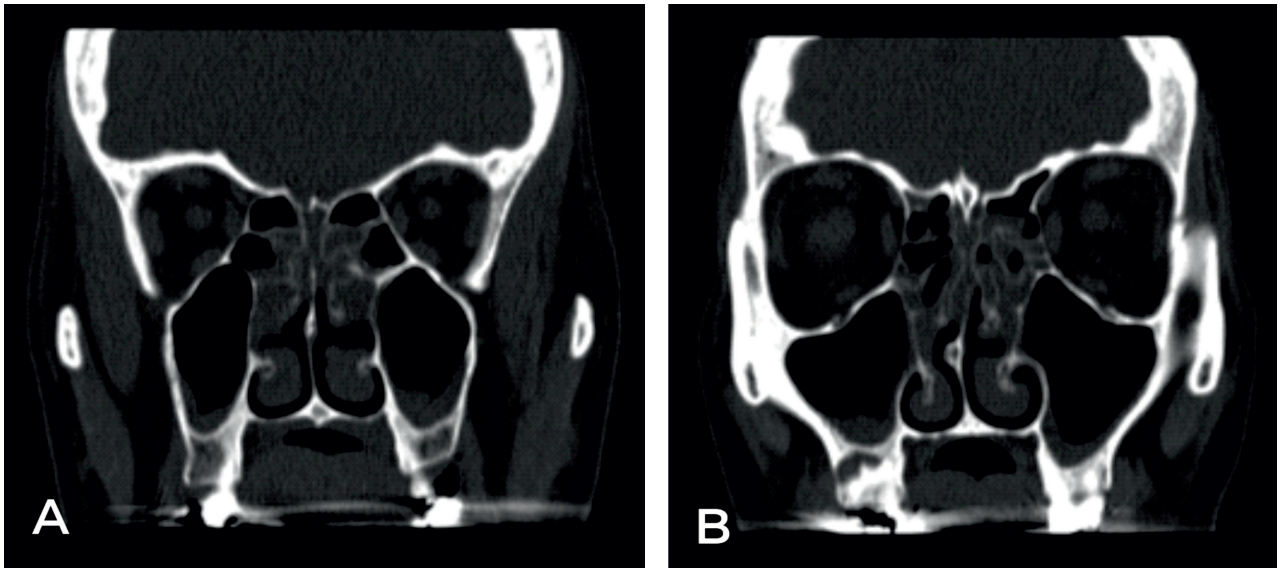


Figure 3
Computed tomography (CT) images showing the typical findings of Chronic Rhinosinusitis with Central Compartment Atopic Disease: (A and B) - Soft tissues of the nasal septum thickened bilaterally due to polypoid edema. Polypoid alterations of the central compartment, causing obstruction of the osteomeatal complex; ethmoid sinuses show medial involvement, but are unobstructed in their medial and lateral portions



without NP). However, this distinction can be difficult when CCAD has already progressed to opacification of the sinuses. In these cases, the key to differentiation of these entities is the presence of polypoid edema of the central compartment, which is not commonly found in non-atopic sinus inflammatory disease[7]. Thus, CRS with NP presents with diffuse NP, but the middle and upper turbinates and nasal septum are usually spared or minimally affected.

Treatment

DelGaudio et al. described a cohort of patients with CCAD who were treated with nasal and oral corticosteroids, antihistamines, antibiotics, and/or immunotherapy[4]. In these patients, medical therapy did not produce complete resolution of symptoms, and post-treatment CT scans showed persistence of the central compartment thickening and, in some cases, pathological involvement of the adjacent sinuses. Thus, the authors advocated the application of endoscopic sinus surgery (ESS) to remove the polypoid alterations in the central compartment[4].

Although surgery is often used to remove polypoid changes and prevent secondary obstructive phenomena, the underlying inhalational allergy must also be suppressed. Even after surgical intervention, medical treatment should continue. It is not uncommon to find patients who do not comply with medical therapy in the postoperative period and are symptomatic, with normal appearance of the sinus cavity and progressive polypoid alterations of the residual turbinates. Thus, the continuation of topical therapies and immunotherapy is essential since the opening of the affected paranasal sinuses exposes the naïve mucosa (previously unaffected) to a greater load of environmental allergens, which can lead to recurrent disease[14].

Grayson et al. postulated that immunotherapy should be given first and surgery postponed until the nasal cavity mucosa is more stable[10]. However, they also stated that when polypoid changes have occurred over an extended period of time, it is unlikely that medical therapy alone will resolve the remodeling that has already occurred. In their patient series, all patients required surgery, as medical treatment was not able to resolve all symptoms. This sequence of treatments achieved a significant improvement in the symptomatology of patients with CCAD. In patients for whom pre- and postoperative SNOT-22 scores were available, the mean score decreased from 40.2 before surgery to 16.3 after surgery[4].

Additional therapies such as omaluzimab (anti-IgE) were considered only for patients who did not tolerate immunotherapy, hyper-IgE states, and/or persistent allergy with failure of immunotherapy[10].

Discussion

CCAD occurs in young individuals with a history of allergy and is often accompanied by local rhinitis and atopic symptoms such as nasal itching, sneezing, and allergic conjunctivitis. Although the relationship between CCAD and allergy has been established[12], the relationship between this disease and asthma is still unclear. Munoz et al.[18] found evidence of an association between asthma and CRS with NP. However, Gelincik et al.[19] were unable to reproduce these findings. Sedaghat et al.[20] followed-up 59 patients with AR and reported that 24 of them developed CRS, and the onset was significantly faster in patients with asthma as a co-morbidity. In the present review, patients with CCAD and co-morbid asthma accounted for about a quarter of the total number of patients with CCAD (25.2%). Schertzer et al.[21] reported an association between CCAD and respiratory epithelial adenomatoid hamartoma (REAH). The authors postulated that REAH may have a similar etiology to CCAD, resulting from long-standing reactive alterations of the mucosa of the central compartment of ethmoid embryological origin.

CCAD should also be differentiated from AERD. Jang et al. demonstrated that the recurrence of AERD frequently occurs in the central

compartment and olfactory region[22]. However, CCAD and AERD are easily distinguishable by the fact that the polyps in CCAD (if present) are aqueous compared to the more fibrous polyps in recurrent AERD. In addition, AERD mainly affects the sinuses in a diffuse pattern. In contrast, CCAD patients do not have aspirin sensitivity and only rarely have asthma, unlike cases of AERD[23].

The studies included in this literature review emphasize the importance of using nasal endoscopy, CT, and histology to accurately diagnose CCAD. This review also explored the current treatment approaches for CCAD, which involve a combination of endoscopic sinonasal surgery to remove the affected mucosa, medical treatment with topical intranasal corticosteroids, and treatment of the underlying allergic pathology with immunotherapy.

This review has some limitations, namely the fact that six of the 13 studies included were retrospective cohorts that depended on the quality of the collected clinical records. Prospective studies are needed to better delineate and understand the environmental and host causes of this subtype of CRS. Secondly, the population included in each study was heterogeneous and the authors did not report the clinical protocol for the follow-up of patients prior to diagnosis. Thirdly, most studies reported the results of a single hospital center, which may affect the generalizability the results, given the large variability of human and material resources among centers. There were also no studies that compared patients of different age groups or with previous comorbidities. Lastly, the follow-up time in the included studies was not long enough to compare the results of different treatments. Furthermore, there are no randomized trials describing therapeutic options depending on the individual characteristics of the patients.

Future studies that reflect the reality of the Portuguese population are necessary, as none of the included studies described this population. In addition, the diagnostic criteria for CCAD have not been defined yet. The role of surgery is still unclear, and more studies are needed to identify which patients may benefit from surgery according to the underlying conditions.

Conclusion

CCAD is a distinct form of CRS, characterized by edematous and polypoid changes in the middle and upper turbinates, as well as the posterosuperior region of the nasal septum. Its pathophysiology is associated with exposure to inhaled allergens. If left untreated, central compartment polypoid disease can progress from the medial to lateral portions, and secondarily obstruct the sinuses. The mechanism responsible for this progression involves the lateral displacement of the middle turbinate or extension of the polyps to the sinus ostia of the sinuses.

The identification of CCAD as a variant of CRS with nasal polyps is important to better understand the role of allergy in CRS and to define the treatment of atopy as central to the management of these patients.

Although there is a growing interest in CCAD, prospective studies are needed to better understand its management and pathophysiology, particularly regarding the surgical interventions and role of allergic disease control.

Conflicts of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

Data Confidentiality

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

Protection of humans and animals

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the 2013 Helsinki Declaration of the World Medical Association.

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Availability of scientific data

There are no datasets available, publicly related to this work.

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