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Original article

The olfactory function in patients with common variable immunodeficiency

G. Magliulo [a,*], G. Iannella [a], A. Ciofalo [a], D. Angeletti [a], F. Pulvirenti [b], I. Quinti [b]

[a] Organi di Senso Department, Sapienza University of Rome, Viale del Policlinico, 151, 00161 Rome, Italy
[b] Department of Molecular Medicine, Sapienza University of Rome, Rome, Italy

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ABSTRACT

Aims: To determine the incidence of olfactory dysfunction in common variable immunodeficiency patients. To evaluate the correlation between olfactory dysfunction and chronic rhinosinusitis in this class of patients.
Materials and methods: Fifty patients, with a diagnosis of common variable immunodeficiency and under immunoglobulin replacement therapy, were submitted to an otolaryngology physical examination and a CT scan of the craniofacial structures in order to show the presence of signs of chronic rhinosinusitis. An olfactory function evaluation was executed using the Sniffin' Sticks Test, with assessment of olfactory threshold, discrimination, identification and overall composite scores (TDI: threshold-discrimination-identification score).
Results: An olfactory dysfunction was found in 23 (46%) common variable immunodeficiency patients, with hyposmia and anosmia respectively present in 65% and 38% of them. The mean TDI score in the study group was 27.7. Common variable immunodeficiency patients with CRS presented a more suggestive increase of the olfactory threshold, discrimination and identification compared to those without chronic rhinosinusitis.
Conclusion: In conclusion, patients with common variable immunodeficiency seem to suffer from olfactory disorders more than healthy people. One of the causal factors could be considered the presence of rhinosinusal pathologies.

1. Introduction

Common variable immunodeficiency (CVID) is the most common form of primary antibody immunodeficiency (PAD) and includes a heterogeneous group of antibody deficiencies, generally diagnosed in adults. It is characterized by decreasing IgG, IgM and/or IgA serum levels, poor or absent antibody response to vaccine, recurrent respiratory tract infection, autoimmunity, gastrointestinal disease and cancer [1,2].

Smell is one of the five sensorineural systems, essential in daily human life for nutrition, sexuality, memory and toxin detection. It improves the quality of life, thanks to recognition of dangerous situations such as spoiled food, fire and gas leaks [3].

The incidence of olfactory dysfunction (OD) has been estimated to be 20% by Hummel et al., in a recent study comprising 3282 healthy subjects, aged between 36 and 55 years [4] and 24.5% in another study comprising subjects over the age of 53 [5].

A variety of conditions are able to influence this sensorineural system: rhinosinusitis, head trauma, neurocognitive disorders, organic disorders (liver and renal disease, autoimmunity, metabolic disease), drugs and toxins [3–6]. Besides, congenital anosmia in isolated or syndromic pathologies has been described [7].

Many of these conditions, in particular high respiratory tract inflammation and infection, are characteristic of common variable immunodeficiency. The frequency of upper respiratory tract diseases in CVID patients ranges between 70% and 98%, with an incidence of 36% of chronic rhinosinusitis (CRS) [1,8,9].

The aims of this prospective observational study were:

- to determine the incidence of olfactory dysfunction in CVID patients;
- to evaluate the correlation between olfactory dysfunction and chronic rhinosinusitis in this class of patients.

* Corresponding author. University La Sapienza of Rome, Via Gregorio VII n. 80, 00165 Rome, Italy.
E-mail address: giuseppemagliuloorl@yahoo.com (G. Magliulo).

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Table 1
Epidemiological and clinical characteristics of 50 CVID patients.

Epidemiological characteristics		
Mean age		44 years
Sex		22 Male28 Female
Clinical characteristics		
Chronic rhinosinusitis		19 (38%)
	Chronic rhinosinusitis without polyposis	15 (30%)
	Sinonasal polyposis	4 (8%)
Rhinosinusal surgery		0

2. Materials and methods

The present prospective observational study was performed at the ENT Unit in collaboration with the Referral Care Center for Adult Immune Deficiency of Sapienza, University of Rome, Italy, between January 2014 and May 2017.

Sixty patients with a previous diagnosis of CVID established according to the ESID/PAGID criteria (Geha, 2007, Quinti I, 2007, Conley, 1999) were initially investigated in terms of ENT medical history and previous surgery of the rhinosinusal tract. An ENT physical examination with nasal endoscopy (2,7 mm 0 degree rigid endoscope) was also performed in order to observe the nasal structures and identify any rhinosinusal pathologies (inflammatory disease, infection, and malignancy).

The exclusion criteria for enrollment in the present study included: asthma, malignancy, neurological and psychiatric diseases, head trauma, metabolic and endocrine pathologies, history of smoking more than 3 cigarettes/day and corticosteroid treatment (both topical and systemic). The presence of acute rhinosinusitis or any prior episode occurring in the previous 3 weeks, as well as surgical reduction of the inferior turbinate, were also considered criteria for exclusion, as they could influence olfactory function.

Fifty patients (22 males and 28 females, 28–81 years of age, average age: 44 years), with a diagnosis of CVID [1,9,10] were considered eligible for this study and were enrolled in the study group.

All these patients were receiving intravenous (IVIG) or subcutaneous immunoglobulin (SCIg) replacement therapy at the time of the study.

The presence of a clinical condition of chronic rhinosinusitis was investigated in CVID patients in accordance with the EPOS classification (2 or more signs and symptoms such as bilateral nasal obstruction, nasal discharge, facial pain/headache, subjective olfactory dysfunction for 12 or more weeks, without their complete resolution) [11]. Besides, all CVID patients enrolled in the study were submitted to an evaluation of the olfactory function and a CT scan of the craniofacial structures, whereas they refused to perform an MRI to evaluate olfactory bulbs/tracts and central olfactory structures.

The same exclusion criteria adopted for the study group were applied to a control group of forty patients (22 males and 18 females, 19–79 years of age, average age: 45years) who did not present CVID or other primary or secondary immunological disorders which underwent the same olfactory evaluation as the study group. The study flow-chart is showed in Fig. 1.

2.1. Epidemiological and clinical characteristics of CVID patients

According to the EPOS classification [11], 19 patients (38%) were classified as having chronic rhinosinusitis with nasal discharge and nasal obstruction and, in particular, 4 (8%) of them presented nasal polyposis at nasal endoscopy (Table 1). All patients with a clinical diagnosis of CRS/nasal polyposis, presented radiological signs of chronic inflammatory rhinosinusal involvement/nasal polyposis at CT scan. None of the patients of the study had undergone rhinosinusal surgery.

2.2. Evaluation of olfactory function

Olfactory perception was evaluated by the Sniffin' Sticks (Bughart, Wedel, Germany) method [12,13]. It consists of a battery of odorant–filled felt pens that release smells and are used to perform three different subtests evaluating olfactory threshold (OT), olfactory discrimination (ODs) and olfactory identification (OI). All subjects are blindfolded to avoid any visual identification of the pens. The olfactory threshold is tested using dilutions of n-butanol in a single-staircase and a triple-forced choice procedure between pen triplets, comprising two blanks and one odorant pen. The discrimination test consists of presentation in random order of triplets of pens with two containing the same odorant and the third a different odorant. The identification capacity is tested through the recognition of 16 odorants presented at suprathreshold intensity using a multiple-choice procedure. The threshold was scored from 1 to 16, while discrimination and identification were scored from 0 to 16. The addition of single scores makes it possible to obtain the TDI score "composite threshold-discrimination-identification score". In the analysis of Sniffin' Sticks tests, a TDI score >30.3 indicates normal olfactory function and perception, a TDI score between 30,3 and 16,5 indicates hyposmia, while a TDI < 16.5 indicates anosmia [12,13].

2.3. CT scan

All CVID patients enrolled in the study were also submitted to CT scan of the craniofacial structures (axial, coronal and sagittal projections, without intravenous contrast injection) at the moment of ENT evaluation in order to identify the presence of chronic rhinosinusitis, nasal polyposis, previous rhinosinusal surgery, nasal malformations or other conditions responsible for olfactory dysfunction. Patients with CVID agreed to undergo craniofacial CT scan without medium contrast because the guidelines for management and treatment of common variable immunodeficiency state that this should be performed in all patient with diagnosed CVID in order to confirm a possible chronic rhinosinusitis [1,9,10]. The craniofacial CT scan was not performed in the control group in order to avoid unnecessary exposure to radiation. All patients gave their written informed consent for taking part in the study and for undergoing the tests and exams mentioned above. This research study was performed in accordance with the principles of the Declaration of Helsinki and approved by the local Ethics Committee of the University "Sapienza" of Rome.

2.4. Statistical analysis

For the analysis of the study data and comparison of data between groups, the Chi^2, Student's T test and regression analysis were performed. Results were expressed as a P value of < 0.05 taken as the threshold of statistical significance.

The Chi^2 test was employed to compare the study group and the control group regarding the presence of olfactory dysfunction and to correlate OD with the CRS. Student's T test it was used to compare data regarding the TDI score between the two groups studied. Using the same test, it was possible to compare the age of patients with and without olfactory dysfunction and the results of olfactory subtesting between the study and control groups. Finally, regression analysis was adopted to investigate a possible relationship between the TDI score and the median age of the study group.

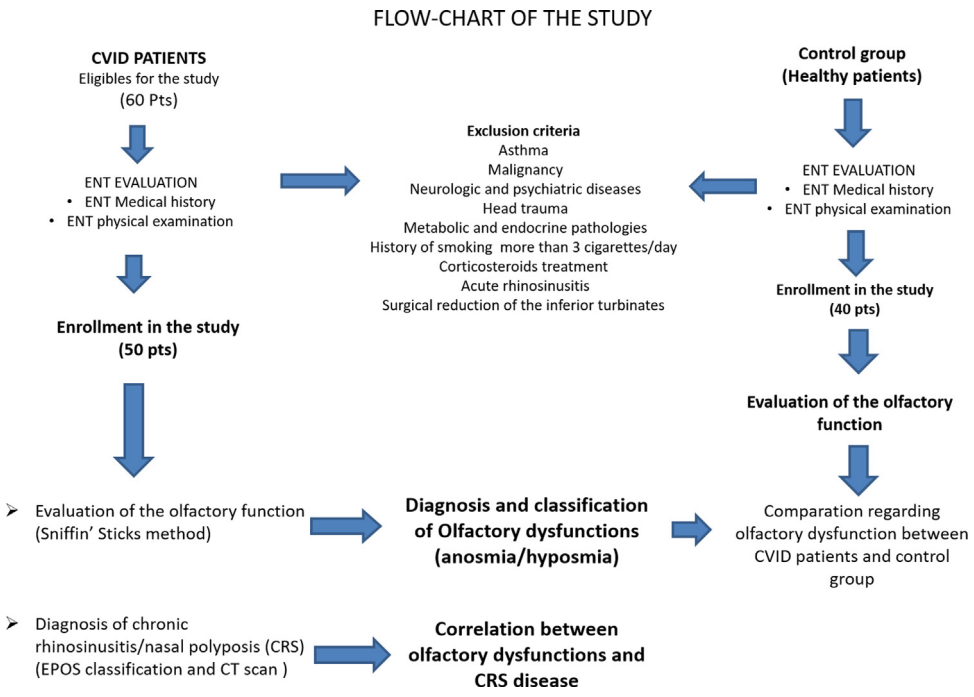

Fig. 1. Flow-chart of the study.

Table 2
Distribution of olfactory dysfunction and mean value of TDI score in CVID patients and control group.

	CVID Group (50 pts)	Control group (40 pts)	*P* value
Olfactory dysfunctionHyposmiaAnosmia	23 (46%)15 (65%)8 (35%)	7 (17.5%)6 (85.7%)1 (14.3%)	*P* = 0.0065
TDI score (Mean value)	27.7	33.3	*P* = 0.005

3. Results

The Sniffin' Sticks test showed the presence of olfactory dysfunction in 23 (46%) CVID patients. Fifteen (65%) of them presented hyposmia and 8 (35%) anosmia. In the control group, only 7 (17,5%) patients had an OD, with a prevalence of hyposmia (85.7%). The comparison between the CVID group and the control one showed a statistically significant difference (*P* = 0,0065) (Table 2).

The mean TDI score in the study group was 27.7 (S.D. = 8.7; Hi = 43,0; Low = 9,0), whereas the mean value of the TDI score in the control group was 33,3 (S.D. = 5,31; Hi = 39.0; Low = 14.0). A statistically significant difference between the two groups (*P* = 0.005) was present (Table 2).

No difference regarding median age emerged between patients with and without olfactory dysfunction (*P* = 0.8). Moreover, regression analysis between the TDI score and median age did not show any statistical correlation (*P* = 0.7).

Thirteen CVID patients presented CRS and OD, accounting for the 56% of the total patients with olfactory dysfunction, whereas 46% of patients with OD did not show CRS. Besides, 77,7% of patients without OD did not show CRS (Fig. 2).

A statistical difference between the sub groups of patients with and without OD and a diagnosis of rhinosinusitis was observed (*P* = 0.02).

Furthermore, the mean value of the single scores (olfactory threshold, olfactory discrimination and olfactory identification) comprised in the TDI score was calculated for CVID patients with smell impairment and signs of rhinosinusitis and for CVID patients without rhinosinusal involvement. The first group presented the following mean values OS = 6.74, OD = 7.53 and OI = 8.26; in the second group without rhinosinusitis mean values of OS = 9.03, OD = 10.71 and OI = 10,87. A comparison of these findings using Student's T-test identified a statistically significant difference between the respective mean value of single scores between the two group of patients (OS: *P* = 0.0260; OD: *P* = 0.011; O: *P* = 0.0016). (Table 3).

4. Discussion

The evaluation of olfaction and its disorders remains difficult in clinical practice. It requires full cooperation of the subject involved and is deeply related to his/her olfactory education and memory.

Many olfactometry techniques have been described in order to investigate the olfaction loss and to characterize an olfactory dysfunction, however, only psychophysical methods are generally used in clinical practice [14,15].

Olfactometry, using chemosensory evoked potentials, is the gold-standard method for investigating the integrity of the olfactory system. This objective test makes it possible to monitor the propagation of olfactory activation in the brain. However, this test is performed only by few specialized institutions because it requires complex equipment, expert operators, and long execution times. Therefore, its use is limited in the evaluation of the olfactory function in clinical practice [3,12,16].

Today, with the magnetic resonance imaging (MRI) and the MRI voxel-based morphometry (VBM) it is possible to evaluate the olfactory bulb/tracts and/or central olfactory structures [16,17].

The olfactory bulb volume evaluated using MRI has been shown to be related to olfactory function in both normal and pathological conditions [13–16]. The authors reported that olfactory bulb volume decreases with the duration of the olfactory loss and that patients with qualitative disorder such as parosmia have smaller olfactory bulbs than patients without parosmia [13–17]. Besides,

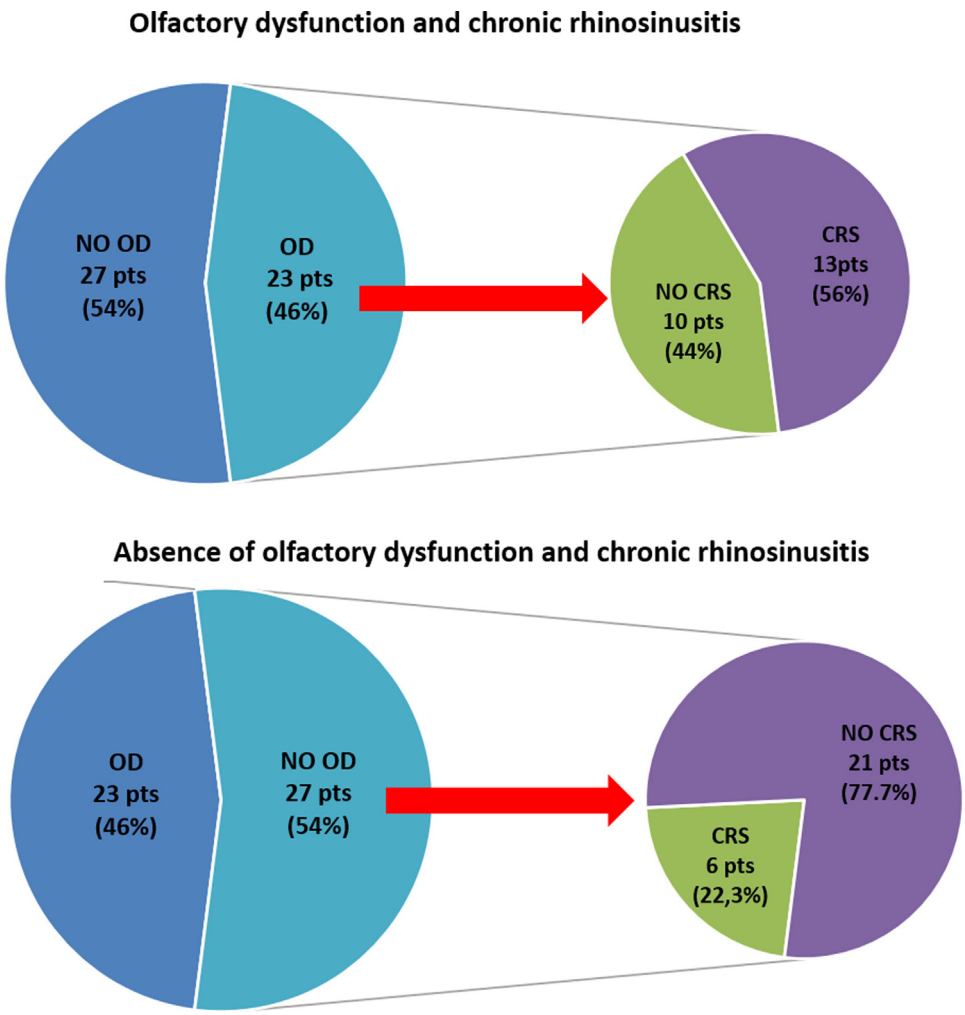

Fig. 2. Pie charts: olfactory dysfunction and chronic rhinosinusitis.

Table 3
Mean value of TDI subtests and diagnosis of rhinosinusitis.

	CVID with Rhinosinusitis	CVID without Rhinosinusitis	*P* value
Olfactory threshold (mean value)	6,74 (SD 3,59)	9,03 (SD 3,33)	0.026
Olfactory discrimination(mean value)	7,53 (SD 3,92)	10,71 (SD 2,58)	0.0011
Olfactory identification (mean value)	8,26 (SD 2,77)	10,87 (SD 2,63)	0.0016

as reported by Goektas et al. [16], there is a very good correlation between the findings of objective olfactometry and bulb volume determined by MRI, whereas no significant association between subjective olfactometry (psychophysical testing) and bulb volume on MRI has been reported. Using MRI VBM, several studies have investigated the relationship between structure of brain and olfactory function in healthy subjects [17,18]. Olfactory performance correlates with both the cortical thickness of distinct structures such as the orbitofrontal cortex (OFC), the insular cortex (IC), and the volume of the right OFC in healthy subjects [17,18].

Despite this evidence, subjective methods such as the Sniffin' Sticks test are generally used in clinical practice to investigate the olfactory function [5,19]. This test allows the assessment of various olfactory functions such as the detection threshold for one or more odours and the ability to identify or discriminate between them [5,17–19]. Besides, it is an essential tool for monitoring the course of these performances in response to physiological ageing or pathological events [5,19].

The CVID population has never been examined in terms of its olfactory function and studies that investigated the incidence of olfactory dysfunction in these patients are not reported in literature. Only Masieri et al. [20] clinically observed the olfactory alteration in such patients, reporting hyposmia in 50% of 22 patients with a diagnosis of CVID. On the other hand, Guilemany et al. [21] found that patients with immunodeficiency and bronchiectasis had an impairment of olfactory function and perception, probably caused by a mechanism of chronic inflammation and obstruction of the rhinosinusal tract.

Differently, the presence of hyposmia in secondary immunodeficiency conditions, such as HIV infections, has been well established. In particular, it was seen that this category of patients had an odour threshold elevation, induced by a viral infection of the rhinosinusal tract with involvement of the olfactory epithelium. In addition, there was a decline of discrimination and identification abilities, most probably related to a reduction of cognitive capacities [22].

The Sniffin' Sticks method was chosen to evaluate the olfactory damage in this study because considered a validated method, widely used in clinical practice, for research purposes [3–5,12,13].

Moreover, CVID patients do not present neurological involvement, central olfactory structure alterations or reduction of cognitive capacities that would be able to alter the results of this test [13].

An olfactory dysfunction was found in 46% of CVID patients in our clinical study.

The above data show that the incidence of an olfactory dysfunction is higher in this class of patients not only in comparison to the patients of the control group in our study (17.5% of patients with OD), but also in comparison to the published data regarding OD in a healthy population [4] (Incidence of OD in 20% of subjects with an age range between 36 and 55 years).

Furthermore, the average TDI score in our study group (27.7) was statistically different to the average TDI of the control group (33.3).

In patients with OD, hyposmia and anosmia were present in 15 patients (65%) and 8 patients (35%) respectively. According to these findings, hyposmia would seem to be the most common olfactory dysfunction in patients with CVID.

Age is an important parameter that might negatively influence the olfactory functions [23]. It has been proven that over the years the olfactory function decreases and reports indicate that more than 75% of people over the age of 80 years show evidence of major olfactory impairment, and that olfaction declines considerably after the seventh decade [23,24].

The median age of enrolled patients was 44 years, thus reflecting a study group in which age-related olfactory damage should be absent.

In our study group, the average patient age was not different from the control group ($P > 0.05$): besides, CVID patients with OD did not present an average age higher than that of patients without OD. Furthermore, regression analysis between the TDI score and mean age did not show any statistical correlation ($P > 0.7$). These data would seem to exclude age as a possible confounding factor of the study and causal factor of OD in this category of patients.

Our results could be explained by considering that CVID has a variable clinical presentation, but most frequently this consists of upper respiratory diseases [1,2,8,9].

Chronic rhinosinusitis in CVID patients has a greater incidence (36%) than in the healthy population (2–16%) [1,8,9,25]. Similar results were observed in our study with 38% of CVID patients classified as having chronic rhinosinusitis.

Chronic rhinosinusitis is a proven causal factor of olfactory loss [26]. Soler et al. [26] using the Sniffin' Sticks test found an incidence ranging 40% to 80% of smell perception disorders in patients with chronic rhinosinusitis.

In our study, 56% of CVID patients with olfactory dysfunction presented clinical and radiological rhinosinusal involvement with a statistical correlation. Besides, CVID was associated with hyposmia in most cases as is often the case in patients who suffer from CRS [26].

There are two areas in the nasal cavity important for smell perception: the olfactory cleft in the superior part of the nose and the area around the inferior turbinate. Odorants are carried by air into the nasal cavity, dissolving in the mucous on the surface of the neuroepithelium of the olfactory cleft, where they bind to G-protein coupled receptors. The nerve impulse propagates to the olfactory bulb and the information is then processed in the primary olfactory cortex and secondary and tertiary centers [27].

Some authors hypothesized that the local absence of plasma cells or IgA and IgM, despite IgG replacement therapy, determines an inflammatory local reaction, induced by the relapse of histamine and other cytokines, in response to external agents [1,2,9]. As a consequence, such patients could present an alteration of mucociliary clearance in the form of an increase in nasal mucociliary transport times [20]. This situation might favour a bacterial colonization, with a high risk of developing rhinosinusal infections and the normal distribution of odorants to the nasal mucosa could be reduced. In this way, the nerve impulse transport to the central olfactory system would be impaired with a deficit of olfactory perception, in particular for smell at threshold level [27].

In our study, an elevation of the olfactory threshold was found and also an impairment of discrimination and identification more suggestive in CVID patients with CRS compared to those without CRS (mean values of OS = 6.74; OD = 7.53 and OI = 8.26 vs. OS = 9.03; OD = 10.71 and OI = 10.87).

Whitcroft et al. [28] found that patients with rhinosinusal disease had an impairment of threshold levels with an increasing value, but a substantial preservation of suprathreshold olfactory performance. Considering this aspect and the non-negligible percentage of CVID patients with OD but without CRS, it seems likely that there are other pathogenetic factors able to induce an olfactory dysfunction in CVID patients. In fact, it is already well-known that olfactory dysfunction is related to autoimmune diseases (Wegener granulomatosis, Churg–Strauss syndrome, systemic lupus erythematosus, Sjögren's syndrome, and systemic sclerosis) [4,6,20]. These autoimmune diseases involve the nasal mucosa and osteocartilaginous structures of the nose and could be the cause of an atrophic rhinitis that would explain OD in these patients [29].

5. Conclusion

Patients with CVID seem to suffer from olfactory disorders more than healthy people and present more often hyposmia; the olfactory damage in these patients involves both odour threshold, discrimination and identification, with a greater impairment in presence of clinical and radiological signs of chronic rhinosinusitis. A limitation of this study could be the absence of an MRI evaluation of these patients. Further studies based on objective olfactory tests in a higher number of patients are necessary to obtain more information about olfactory damage in patients with primary antibody immunodeficiency.

Ethics approval and consent to participate

The ethics committee of the Sapienza University of Rome approved the study. All procedures of this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from the patient who participated in this case report.

Disclosure of interest

The authors declare that they have no competing interest.

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