**Name of Journal:** *World Journal of Methodology*

**Manuscript NO:** 61824

**Manuscript Type:** MINIREVIEWS

**Olfactory dysfunction in antineutrophil cytoplasmic antibody-associated vasculitides: A review of the literature**

Pendolino AL *et al*. Sense of smell and ANCA-associated vasculitides

Alfonso Luca Pendolino, Anika Kaura, Annakan V Navaratnam, Monica Pendolino, Gerolamo Bianchi, Samit Unadkat, Giancarlo Ottaviano, Premjit S Randhawa, Peter J Andrews

**Alfonso Luca Pendolino, Anika Kaura, Annakan V Navaratnam, Samit Unadkat, Premjit S Randhawa, Peter J Andrews,** Department of Ear, Nose and Throat, Royal National ENT and Eastman Dental Hospitals, London WC1E 6DG, United Kingdom

**Alfonso Luca Pendolino, Anika Kaura, Peter J Andrews,** Ear Institute, University College London, London WC1X 8EE, United Kingdom

**Monica Pendolino, Gerolamo Bianchi,** Division of Rheumatology, Department of Locomotor System, ASL 3, Genoa 16121, Italy

**Giancarlo Ottaviano,** Department of Neurosciences DNS, Otolaryngology Section, University of Padua, Padua 35128, Italy

**Author contributions:** Pendolino AL designed the study, performed the literature search and wrote the paper; Kaura A prepared the table and reviewed the paper; Navaratnam AV, Pendolino M, Bianchi G, Unadkat S, Randhawa PS and Ottaviano G reviewed the paper; Andrews PJ coordinated the writing of the paper and reviewed the final version.

**Corresponding author: Alfonso Luca Pendolino, MD, Academic Fellow, Surgeon,** Department of Ear, Nose and Throat, Royal National ENT and Eastman Dental Hospitals, 47-49 Huntley Street, Bloomsbury, London WC1E 6DG, United Kingdom. alfonso.pendolino@nhs.net

**Received:** December 19, 2020

**Revised:** January 2, 2021

**Accepted:** February 19, 2021

**Published online:**

**Abstract**

Olfactory dysfunction (OD) has been described in patients with antineutrophil cytoplasmic antibody-associated vasculitides (AAV), but the underlying mechanisms are not completely understood. The causes of altered smell function can generally be divided into conductive, sensorineural or others. To date no specific treatment is available for AAV-related OD and the efficacy of currently available options has not been explored. The aim of this review is to provide an overview of the causes that may lead to OD in patients with AAV. Current available treatments for OD and possible options in patients with AAV presenting with smell impairment are also mentioned.

**Key Words:** Smell; Olfactory dysfunction; Antineutrophil cytoplasmic antibody-associated vasculitis diseases; Granulomatosis with polyangiitis; Eosinophilic granulomatosis with polyangiitis; Microscopic polyangiitis

Pendolino AL, Kaura A, Navaratnam AV, Pendolino M, Bianchi G, Unadkat S, Ottaviano G, Randhawa PS, Andrews PJ. Olfactory dysfunction in antineutrophil cytoplasmic antibody-associated vasculitides: A review of the literature. *World J Methodol* 2021; In press

**Core Tip:** Olfactory dysfunction may develop during the course of antineutrophil cytoplasmic antibody-associated vasculitides. Typically, this is caused by a combination of active and chronic sinonasal inflammation causing necrosis and atrophic changes in the nasal mucosa, sensorineural involvement as well as other systemic factors. Systemic treatment of the vasculitis, control of coexisting rhinosinusitis, and management of nasal complications are recommended and could lead to an improvement in olfactory function.

**INTRODUCTION**

The antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are multi-system autoimmune disorders, characterised by necrotising inflammation of the small to medium sized vessels with the presence of serum antibodies targeting cytoplasmic components of neutrophils. These antibodies specifically target proteinase 3 (PR3) and myeloperoxidase (MPO), contributing to a cytoplasmic or perinuclear pattern in indirect immunofluorescence staining respectively.

The American College of Rheumatology in 1990 classified granulomatous diseases into either granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA)[1,2]. Further to this, definitions for AAV were formulated at the Chapel Hill Consensus Conference in 1994 and later revised in 2012 and comprise GPA, EGPA and microscopic polyangiitis[3].

Ear, nose and throat involvement has been reported to be the second most common site after the lungs, and often precedes the diagnosis of AAV by many months[4]. The nose and paranasal sinuses, in particular, are the most frequently affected sites in the head and neck, representing 64% to 80% of the cases. Of importance, the nose has been shown to be the only affected site in about 30% of the GPA patients and hence a high index of suspicion is warranted[5].

Common manifestations of AAV in the nose include epistaxis, crusting and nasal polyps, or septal perforation and saddle nose deformity in the more severe cases. Impairment of sense of smell has also been described in patients with AAV, but the mechanisms underlying the olfactory dysfunction (OD) are not completely understood.

The aim of this review is to provide an overview of the causes that can lead to OD in patients with AAV. Current available treatments for OD and possible options in patients with AAV presenting with smell impairment are also mentioned.

**CURRENT FINDINGS ON OLFACTORY DYSFUNCTION IN ANCA-ASSOCIATED VASCULITIDES**

The involvement of the olfactory system in AAV has been reported by several authors, even if most of the available findings refer to GPA. Subjective assessment of olfaction and taste showed that patients with GPA are aware of their diminished chemosensory functions[6].Göktas *et al*[7] found that chemical senses (*i.e.* olfactory, gustatory and trigeminal functions) are affected consistently and to a similar extent in GPA patients when they are assessed by means of psychophysical tests [*e.g.* Sniffin’ sticks or the University of Pennsylvania Smell Identification Test][7]. Proft *et al*[8] observed that 75% of their patients with GPA were found to be hyposmic at Sniffin’ sticks; a similar prevalence of olfactory impairment (74%) in GPA patients was also reported by Zycinska *et al*[9]. In a retrospective analysis conducted on 230 GPA patients, Kühn *et al*[10] found that the majority of them were hyposmic (62%) with only 18% showing a preserved sense of smell (normosmia) and 20% having a complete smell loss (anosmia). Fasunla *et al*[6] found that GPA patients were hyposmic with reduced scores in all the olfactory subset tests (identification, discrimination and threshold) when compared to the sex and age-matched healthy control group. These finding were later replicated by other authors[8,9,11].

Very little has been published on olfactory dysfunction in EGPA patients. In 2014 Tallab *et al*[12] reported a case of EGPA presenting with total loss of sense of smell measured by University of Pennsylvania Smell Identification Test, which appeared before the onset of other disease symptoms, suggesting that OD may precede the clinical symptoms[12].

To the best of our knowledge no cases of OD have been described in patients with microscopic polyangiitis.

**CAUSES OF OLFACTORY DYSFUNCTION**

The lower scores found by several authors in both the identification, discrimination and threshold olfactory subsets tests[8,9] may suggest that mechanisms leading to OD in AAV could be multifactorial[13].

Causes of altered olfactory function can generally be divided into: (1) conductive, which include recurrent sinonasal inflammation, crusting, granuloma formation, bone structure damage, necrosis or atrophic changes in the mucous membrane; (2) sensorineural, with a central or a peripheral neural involvement (focal ischemic changes and cranial nerve damage); and (3) other factors, including systemic factors, concurrent surgery, the use of local (antibiotic ointments) or systemic immunosuppressive drugs[11].

However, and this is probably the most common situation, OD may result as a combination of two or more of the previously described mechanisms. Table 1 summarises the causes and mechanisms involved in the development of AAV-OD.

**OLFACTORY DYSFUNCTION DUE TO CONDUCTIVE CAUSES**

Sinonasal involvement has been reported to be the most frequent ear, nose and throat manifestation in patients with GPA[14]. Nasal ulceration, crusting and scarring are frequently seen in patients with AAV, especially in GPA[10], and in turn may cause a mechanical obstruction for odorants to reach the olfactory cleft, thus contributing to an altered sense of smell. However, Proft *et al*[8] found no correlation between OD and the aforementioned nasal manifestations, indicating that the decrease in olfactory function could be a consequence of the inflammatory disease in the nose rather than the local manifestation (bloody nasal discharge, crusts, granulomata). Similarly, none of the patients with localised disease had a higher degree of OD[11]. Therefore, active and chronic inflammation (rhinosinusitis) in GPA patients seems to be the more likely cause for the reported OD[9]. Due to the peculiar location of the olfactory fibres in the nose, smell impairment can result as an extension of the mucosal inflammation in the olfactory cleft and to the olfactory receptor cells. Reduction of sense of smell, in fact, is frequently reported in patients with chronic rhinosinusitis (CRS) and it is one of the main symptoms that can aid diagnosis of CRS[14].As a confirmation of that, OD has been found to be common in GPA patients with increased crusting, pathological granulation but also a higher Lund-MacKay score (a score used for radiologic staging of CRS)[9].

Additionally, the colonisation of the affected nasal mucosa with bacteria such as Staphylococcus aureus may lead to recurrent nasal infections and further nasal inflammation. Having said that, no correlation between olfactory function and colonisation with Staphylococcus aureus was found[15].

Finally, septal perforations (commonly found in the more severe cases of GPA) can potentially cause OD by altering the flow of air and odour molecules into the olfactory cleft. However, Fasunla *et al*[6] did not identify any significant difference in olfactory performance assessed by means of Sniffin’ Sticks (TDI score) between patients with or without septal perforation[6].

**OLFACTORY DYSFUNCTION DUE TO SENSORINEURAL CAUSES**

Cranial nerve involvement in patients with AAV is widely described[16-18]. In particular, GPA has repeatedly been associated with peripheral and cranial nerve neuropathies[16]. Fauci *et al*[17] found that 7.4% (8/85) of GPA patients had cranial nerve involvement whereas Nishino *et al*[18] reported a lower prevalence of 6.5% in their retrospective series of 324 GPA patients. Nevertheless, involvement of the first cranial nerve seems to be rare[18]. Theoretically, the olfactory nerve may be either involved by (1) continuity, especially from nasal and skull base granulomas that can influence the neural transduction in afferent pathways; (2) by vasculitic involvement of small vessels surrounding the cranial nerves, resulting in mononeuritis multiplex; and (3) by the adverse influences of the disease on neurotransmitter systems involved in sensory modulation[12,18].

**OTHER FACTORS INFLUENCING OLFACTORY FUNCTION**

As with other autoimmune diseases, systemic factors could contribute to a lowering of the chemosensory function[19-21]. The active autoimmune processes and the linked cytokine secretion can potentially create a pro-inflammatory environment which can lead to olfactory neuronal damage, subsequent neuronal apoptosis[22] and finally leading to an olfactory function limitation. This hypothesis is supported by previous data from mice models, which showed that proinflammatory cytokines, like the tumour necrosis factor, can directly alter olfactory neuron function[23] and suppress neuroepithelial regeneration[24]. Moreover, lower scores from smell tests have been reported in GPA patients with elevated C-reactive protein values[8]. However, due to the lack of data in GPA patients undergoing olfactory epithelial biopsies, no definitive conclusions can be drawn on the role of immunologic mechanisms in OD in GPA patients or, more generally, in AAV.

Renal insufficiency is known to alter sense of smell[25] and renal function is commonly impaired in patients with AAV. Thus, this could account for OD in AAV patients. However, even though some authors have observed that non-AAV patients with chronic renal failure show OD with lower identification, discrimination and thresholds scores[25,26], no correlation between kidney involvement and smell function was found in GPA patients[6,8,11]. Similarly, no correlation between other organ involvement (eyes, ear, nose, throat, lung, or kidneys) and olfactory function has been reported in the same population[8,11].

The role of disease severity and duration in olfactory impairment is still not clear. Proft *et al*[8]found that GPA patients with a higher extent of damage (measured by the Vasculitis Damage Index score) showed a tendency for reduced scores only for the threshold, but not for the identification, the discrimination or the total score (TDI score) at Sniffin’ sticks. Conversely, neither the disease duration nor the age appear to influence smell function[7].

Drug-induced OD has been widely described[27-29]. Damage to the chemosensory functions secondary to immunomodulatory drugs has been reported by different authors although the exact mechanism through which these drugs can induce olfactory damage is unclear. An impairment of fast regenerating tissue (olfactory epithelium) by chemotherapeutic agents has been hypothesised[8,30]. Furthermore, the role of the tumour necrosis factor-alpha-inhibitors or methotrexate on smell was investigated in patients suffering from rheumatoid arthritis but no significant differences in smell between users and non-users of these medications were found[31]. Nevertheless, GPA patients under therapy with azathioprine showed significantly lower scores only for odour discrimination at the Sniffin’ sticks subtest[8]. Conversely, Tallab *et al*[12] reported a subjective improvement of smell and taste function after immunosuppressive therapy in a patient with EGPA.

Mupirocin is commonly used as a topical antibiotic in AAV patients presenting with crusting and recurrent nasal infections. In this regard, no olfactory dysfunction was observed by Laudien *et al*[11] in 25 GPA patients receiving local mupirocin treatment.

Oral glucocorticoids (GC) represent a keystone in medical treatment in patients with AAV. While systemic GC improve the sense of smell in patients with rhinosinusitis[28] and high dose GC is used to treat olfactory disorders[32,33], low-dose GC has been shown to probably reduce the peripheral olfactory function[31]. Proft *et al*[8] found that GPA patients undergoing low-dose GC therapy showed a tendency for lower thresholds scores compared to patients without GC therapy. Similarly, low-dose GC in rheumatoid arthritis significantly affects thresholds and TDI scores, but not odour identification and discrimination[31].

Finally, the prolonged and complicated wound healing observed in some AAV patients undergoing nasal surgery could lead to an impairment of the chemosensory function. However, Fasunla *et al*[6] did not find any significant difference in sense of smell when GPA patients with and without past history of sinonasal operations were compared.

**Current available treatments**

To date no specific treatment is available for AAV-related OD and the efficacy of treatment options currently adopted for smell impairment has not been explored. Moreover, the lack of a deep understanding of the underlying mechanisms leading to smell loss in this category of patients is limiting the development of more targeted therapies.

In our experience, if a patient presents with nasal crusting or epistaxis, control of the nasal manifestations should be first achieved to rule out any mechanical obstruction (conductive cause) leading to smell impairment. If polyps or mucosal oedema are present, the use of GC, either systemically or topical, should be considered in order to reduce the inflammatory component[33]. However, while indications for oral GC for OD in AAV patients may be reviewed in light of the previously described findings[8,31], the use of topical GC should be weighed up in patients presenting with crusting and epistaxis due to the possibility of an increased risk of bleeding and mucosal dryness with subsequent crusting and local infections. Management of septal perforations, either conservatively or surgically[34,35], should be considered due to the possible relationship between airflow alteration and the consequent obstacle for odour molecules to reach the olfactory cleft. Importantly, if surgical closure of the perforation is planned, it should only be performed when the disease is in remission so as to minimise complications[34].

Smell training can also be considered a potential therapy in AAV patients reporting persistent smell impairment, especially where no other conductive causes can be identified. It is a cost-effective and safe therapy which involves repeated and deliberate sniffing of a set of odorants (commonly lemon, rose, cloves, and eucalyptus) for 20 s each, at least twice a day for a minimum of 3 mo. Smell training is currently recommended in patients with olfactory loss from several aetiologies, even if its effectiveness in patients with AAV has not been explored so far[33].

Other treatments, including phosphodiesterase inhibitors, intranasal calcium buffers, vitamin A, zinc or multivitamins have been described but they are not routinely recommended because of the lack of sufficient evidence[33].

**CONCLUSION**

This review confirms that OD may develop during the course of AAV. The current literature suggests that olfactory impairment is more frequent in patients with GPA, although a possible bias related to the scarcity of papers about smell loss in patients with EGPA and MPA must be taken into account.

Several mechanisms can lead to smell loss in AAV patients, and in most cases, this arises from a combination of different causes. Systemic treatment of the vasculitis, control of a coexisting rhinosinusitis, and management of nasal complications may improve olfactory function, and should be considered in all patients. To date no specific treatment for olfactory improvement in this particular group of patients has been identified. In the future, cytological and histological studies of the affected olfactory mucosa should be encouraged in order to better understand the mechanisms underlying the OD in AAV.

**REFERENCES**

1 **Leavitt RY**, Fauci AS, Bloch DA, Michel BA, Hunder GG, Arend WP, Calabrese LH, Fries JF, Lie JT, Lightfoot RW Jr. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. *Arthritis Rheum* 1990; **33**: 1101-1107 [PMID: 2202308 DOI: 10.1002/art.1780330807]

2 **Masi AT**, Hunder GG, Lie JT, Michel BA, Bloch DA, Arend WP, Calabrese LH, Edworthy SM, Fauci AS, Leavitt RY. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). *Arthritis Rheum* 1990; **33**: 1094-1100 [PMID: 2202307 DOI: 10.1002/art.1780330806]

3 **Jennette JC**, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, Flores-Suarez LF, Gross WL, Guillevin L, Hagen EC, Hoffman GS, Jayne DR, Kallenberg CG, Lamprecht P, Langford CA, Luqmani RA, Mahr AD, Matteson EL, Merkel PA, Ozen S, Pusey CD, Rasmussen N, Rees AJ, Scott DG, Specks U, Stone JH, Takahashi K, Watts RA. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum* 2013; **65**: 1-11 [PMID: 23045170 DOI: 10.1002/art.37715]

4 **Wojciechowska J**, KręCicki T. Clinical characteristics of patients with granulomatosis with polyangiitis and microscopic polyangiitis in ENT practice: a comparative analysis. *Acta Otorhinolaryngol Ital* 2018; **38**: 517-527 [PMID: 30623897 DOI: 10.14639/0392-100X-1776]

5 **Alam DS**, Seth R, Sindwani R, Woodson EA, Rajasekaran K. Upper airway manifestations of granulomatosis with polyangiitis. *Cleve Clin J Med* 2012; **79 Suppl 3**: S16-S21 [PMID: 23203639 DOI: 10.3949/ccjm.79.s3.04]

6 **Fasunla JA**, Hundt W, Lutz J, Förger F, Thürmel K, Steinbach S. Evaluation of smell and taste in patients with Wegener's granulomatosis. *Eur Arch Otorhinolaryngol* 2012; **269**: 179-186 [PMID: 21748655 DOI: 10.1007/s00405-011-1691-y]

7 **Göktas O**, Cao Van H, Fleiner F, Lacroix JS, Landis BN. Chemosensory function in Wegener's granulomatosis: a preliminary report. *Eur Arch Otorhinolaryngol* 2010; **267**: 1089-1093 [PMID: 20043173 DOI: 10.1007/s00405-009-1184-4]

8 **Proft F**, Steinbach S, Dechant C, Witt M, Reindl C, Schulz S, Vielhauer V, Hilge R, Laubender RP, Manger K, Nüsslein H, Wendler J, Schuch F, Schulze-Koops H, Grunke M. Gustatory and olfactory function in patients with granulomatosis with polyangiitis (Wegener's). *Scand J Rheumatol* 2014; **43**: 512-518 [PMID: 25204208 DOI: 10.3109/03009742.2014.915056]

9 **Zycinska K**, Straburzynski M, Nitsch-Osuch A, Krupa R, Hadzik-Błaszczyk M, Cieplak M, Wardyn K. Prevalence of Olfactory Impairment in Granulomatosis with Polyangiitis. *Adv Exp Med Biol* 2016; **878**: 1-7 [PMID: 26269029 DOI: 10.1007/5584\_2015\_164]

10 **Kühn D**, Hospowsky C, Both M, Hey M, Laudien M. Manifestation of granulomatosis with polyangiitis in head and neck. *Clin Exp Rheumatol* 2018; **36 Suppl 111**: 78-84 [PMID: 29799391]

11 **Laudien M**, Lamprecht P, Hedderich J, Holle J, Ambrosch P. Olfactory dysfunction in Wegener's granulomatosis. *Rhinology* 2009; **47**: 254-259 [PMID: 19839246 DOI: 10.4193/Rhin08.159]

12 **Tallab HF**, Doty RL. Anosmia and hypogeusia in Churg-Strauss syndrome. *BMJ Case Rep* 2014; **2014** [PMID: 24825557 DOI: 10.1136/bcr-2014-203959]

13 **Whitcroft KL**, Cuevas M, Haehner A, Hummel T. Patterns of olfactory impairment reflect underlying disease etiology. *Laryngoscope* 2017; **127**: 291-295 [PMID: 27556251 DOI: 10.1002/lary.26229]

14 **Fokkens WJ**, Lund VJ, Hopkins C, Hellings PW, Kern R, Reitsma S, Toppila-Salmi S, Bernal-Sprekelsen M, Mullol J, Alobid I, Terezinha Anselmo-Lima W, Bachert C, Baroody F, von Buchwald C, Cervin A, Cohen N, Constantinidis J, De Gabory L, Desrosiers M, Diamant Z, Douglas RG, Gevaert PH, Hafner A, Harvey RJ, Joos GF, Kalogjera L, Knill A, Kocks JH, Landis BN, Limpens J, Lebeer S, Lourenco O, Meco C, Matricardi PM, O'Mahony L, Philpott CM, Ryan D, Schlosser R, Senior B, Smith TL, Teeling T, Tomazic PV, Wang DY, Wang D, Zhang L, Agius AM, Ahlstrom-Emanuelsson C, Alabri R, Albu S, Alhabash S, Aleksic A, Aloulah M, Al-Qudah M, Alsaleh S, Baban MA, Baudoin T, Balvers T, Battaglia P, Bedoya JD, Beule A, Bofares KM, Braverman I, Brozek-Madry E, Richard B, Callejas C, Carrie S, Caulley L, Chussi D, de Corso E, Coste A, El Hadi U, Elfarouk A, Eloy PH, Farrokhi S, Felisati G, Ferrari MD, Fishchuk R, Grayson W, Goncalves PM, Grdinic B, Grgic V, Hamizan AW, Heinichen JV, Husain S, Ping TI, Ivaska J, Jakimovska F, Jovancevic L, Kakande E, Kamel R, Karpischenko S, Kariyawasam HH, Kawauchi H, Kjeldsen A, Klimek L, Krzeski A, Kopacheva Barsova G, Kim SW, Lal D, Letort JJ, Lopatin A, Mahdjoubi A, Mesbahi A, Netkovski J, Nyenbue Tshipukane D, Obando-Valverde A, Okano M, Onerci M, Ong YK, Orlandi R, Otori N, Ouennoughy K, Ozkan M, Peric A, Plzak J, Prokopakis E, Prepageran N, Psaltis A, Pugin B, Raftopulos M, Rombaux P, Riechelmann H, Sahtout S, Sarafoleanu CC, Searyoh K, Rhee CS, Shi J, Shkoukani M, Shukuryan AK, Sicak M, Smyth D, Sindvongs K, Soklic Kosak T, Stjarne P, Sutikno B, Steinsvag S, Tantilipikorn P, Thanaviratananich S, Tran T, Urbancic J, Valiulius A, Vasquez de Aparicio C, Vicheva D, Virkkula PM, Vicente G, Voegels R, Wagenmann MM, Wardani RS, Welge-Lussen A, Witterick I, Wright E, Zabolotniy D, Zsolt B, Zwetsloot CP. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. *Rhinology* 2020; **58**: 1-464 [PMID: 32077450 DOI: 10.4193/Rhin20.600]

15 **Laudien M**, Gadola SD, Podschun R, Hedderich J, Paulsen J, Reinhold-Keller E, Csernok E, Ambrosch P, Hellmich B, Moosig F, Gross WL, Sahly H, Lamprecht P. Nasal carriage of Staphylococcus aureus and endonasal activity in Wegener s granulomatosis as compared to rheumatoid arthritis and chronic Rhinosinusitis with nasal polyps. *Clin Exp Rheumatol* 2010; **28**: 51-55 [PMID: 20412703]

16 **de Groot K**, Schmidt DK, Arlt AC, Gross WL, Reinhold-Keller E. Standardized neurologic evaluations of 128 patients with Wegener granulomatosis. *Arch Neurol* 2001; **58**: 1215-1221 [PMID: 11493161 DOI: 10.1001/archneur.58.8.1215]

17 **Fauci AS**, Haynes BF, Katz P, Wolff SM. Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. *Ann Intern Med* 1983; **98**: 76-85 [PMID: 6336643 DOI: 10.7326/0003-4819-98-1-76]

18 **Nishino H**, Rubino FA, DeRemee RA, Swanson JW, Parisi JE. Neurological involvement in Wegener's granulomatosis: an analysis of 324 consecutive patients at the Mayo Clinic. *Ann Neurol* 1993; **33**: 4-9 [PMID: 8388187 DOI: 10.1002/ana.410330103]

19 **Delaney P**, Henkin RI, Manz H, Satterly RA, Bauer H. Olfactory sarcoidosis. Report of five cases and review of the literature. *Arch Otolaryngol* 1977; **103**: 717-724 [PMID: 588127 DOI: 10.1001/archotol.1977.00780290053006]

20 **Rasmussen N**, Brofeldt S, Manthorpe R. Smell and nasal findings in patients with primary Sjögren's syndrome. *Scand J Rheumatol Suppl* 1986; **61**: 142-145 [PMID: 3473623]

21 **Shoenfeld N**, Agmon-Levin N, Flitman-Katzevman I, Paran D, Katz BS, Kivity S, Langevitz P, Zandman-Goddard G, Shoenfeld Y. The sense of smell in systemic lupus erythematosus. *Arthritis Rheum* 2009; **60**: 1484-1487 [PMID: 19404932 DOI: 10.1002/art.24491]

22 **Ge Y**, Tsukatani T, Nishimura T, Furukawa M, Miwa T. Cell death of olfactory receptor neurons in a rat with nasosinusitis infected artificially with Staphylococcus. *Chem Senses* 2002; **27**: 521-527 [PMID: 12142328 DOI: 10.1093/chemse/27.6.521]

23 **Sultan B**, May LA, Lane AP. The role of TNF-α in inflammatory olfactory loss. *Laryngoscope* 2011; **121**: 2481-2486 [PMID: 21882204 DOI: 10.1002/lary.22190]

24 **Turner JH**, Liang KL, May L, Lane AP. Tumor necrosis factor alpha inhibits olfactory regeneration in a transgenic model of chronic rhinosinusitis-associated olfactory loss. *Am J Rhinol Allergy* 2010; **24**: 336-340 [PMID: 21243089 DOI: 10.2500/ajra.2010.24.3498]

25 **Frasnelli JA**, Temmel AF, Quint C, Oberbauer R, Hummel T. Olfactory function in chronic renal failure. *Am J Rhinol* 2002; **16**: 275-279 [PMID: 12422973]

26 **Griep MI**, Van der Niepen P, Sennesael JJ, Mets TF, Massart DL, Verbeelen DL. Odour perception in chronic renal disease. *Nephrol Dial Transplant* 1997; **12**: 2093-2098 [PMID: 9351071 DOI: 10.1093/ndt/12.10.2093]

27 **Doty RL**, Shah M, Bromley SM. Drug-induced taste disorders. *Drug Saf* 2008; **31**: 199-215 [PMID: 18302445 DOI: 10.2165/00002018-200831030-00002]

28 **Doty RL**, Bromley SM. Effects of drugs on olfaction and taste. *Otolaryngol Clin North Am* 2004; **37**: 1229-1254 [PMID: 15563912 DOI: 10.1016/j.otc.2004.05.002]

29 **Henkin RI**. Drug-induced taste and smell disorders. Incidence, mechanisms and management related primarily to treatment of sensory receptor dysfunction. *Drug Saf* 1994; **11**: 318-377 [PMID: 7873092 DOI: 10.2165/00002018-199411050-00004]

30 **Wickham RS**, Rehwaldt M, Kefer C, Shott S, Abbas K, Glynn-Tucker E, Potter C, Blendowski C. Taste changes experienced by patients receiving chemotherapy. *Oncol Nurs Forum* 1999; **26**: 697-706 [PMID: 10337648]

31 **Steinbach S**, Proft F, Schulze-Koops H, Hundt W, Heinrich P, Schulz S, Gruenke M. Gustatory and olfactory function in rheumatoid arthritis. *Scand J Rheumatol* 2011; **40**: 169-177 [PMID: 21077800 DOI: 10.3109/03009742.2010.517547]

32 **Steinbach S**, Hundt W, Zahnert T. [The sense of smell in daily life]. *Laryngorhinootologie* 2008; **87**: 657-68; quiz 669-72 [PMID: 18726864 DOI: 10.1055/s-2008-1077547]

33 **Hummel T**, Whitcroft KL, Andrews P, Altundag A, Cinghi C, Costanzo RM, Damm M, Frasnelli J, Gudziol H, Gupta N, Haehne A, Holbrook E, Hong SC, Hornung D, Hüttenbrink KB, Kamel R, Kobayashi M, Konstantinidis I, Landis BN, Leopold DA, Macchi A, Miwa T, Moesges R, Mullol J, Mueller CA, Ottaviano G, Passali GC, Philpott C, Pinto JM, Ramakrishnan VJ, Rombaux P, Roth Y, Schlosser RA, Shu B, Soler G, Stjärne P, Stuck BA, Vodicka J, Welge-Luessen A. Position paper on olfactory dysfunction. *Rhinol Suppl* 2017; **54**: 1-30 [PMID: 29528615 DOI: 10.4193/Rhino16.248]

34 **Pendolino AL**, Unadkat S, Zhang H, Pendolino M, Bianchi G, Randhawa PS, Andrews PJ. The role of surgery in antineutrophil cytoplasmic antibody-associated vasculitides affecting the nose and sinuses: A systematic review. *SAGE Open Med* 2020; **8**: 2050312120936731 [PMID: 32676189 DOI: 10.1177/2050312120936731]

35 **Unadkat SN**, Pendolino AL, Kwame I, Swift A, Pusey C, Gantous A, Andrews PJ. Nasal reconstructive surgery for vasculitis affecting the nose: our two-centre international experience. *Eur Arch Otorhinolaryngol* 2020; **277**: 3059-3066 [PMID: 32623509 DOI: 10.1007/s00405-020-06180-8]

**Footnotes**

**Conflict-of-interest statement:** There is no conflict of interest associated with any of the senior author or other co-authors contributed their efforts in this manuscript.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Peer-review started:** December 19, 2020

**First decision:** December 31, 2020

**Article in press:**

**Specialty type:** Medical laboratory technology

**Country/Territory of origin:** United Kingdom

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Rolla G **S-Editor:** Zhang L **L-Editor: P-Editor:**

**Table 1 Causes and mechanisms involved in the development of antineutrophil cytoplasmic antibody-associated vasculitides olfactory dysfunction**

|  |  |  |
| --- | --- | --- |
| **Ref.** | **Population** | **Findings** |
| Conductive causes | | |
| Laudien *et al*[11], 2009 | 76 GPA patients | No correlation between localised disease and a higher degree of olfactory dysfunction |
| Laudien *et al*[15], 2010 | 89 GPA patients | No correlation between olfactory function and colonisation with Staphylococcus aureus |
| Fasunla *et al*[6], 2012 | 16 GPA patients | No difference in the olfactory performance between patients with and without septal perforation |
| Proft *et al*[8], 2014 | 44 GPA patients | Decrease in olfactory function could be a consequence of the inflammatory disease in the nose rather than the local manifestations (bloody nasal discharge, crusting, granulomata) |
| Zycinska *et al*[9], 2016 | 43 GPA patients | Active and chronic sinonasal inflammation (rhinosinusitis) in GPA patients seems to be the more likely cause for the reported olfactory dysfunction. Olfactory dysfunction is more common in GPA patients with increased crusting, pathological granulation but also a higher Lund-MacKay score |
| Sensorineural causes | | |
| Fauci *et al*[17], 1983 | 85 GPA patients | Cranial nerve involvement reported in 7.4% of GPA patients |
| Nishino *et al*[18], 1993 | 324 GPA patients | Cranial nerves involvement reported in 6.5% of GPA patients even if first cranial nerve was rarely involved |
| Other factors | | |
| Laudien *et al*[11], 2009 | 76 GPA patients | GPA patients receiving local mupirocin treatment showed no olfactory dysfunction. No correlation between kidney involvement and smell function |
| Göktas *et al*[7], 2010 | 9 GPA patients | Neither the disease duration nor the age appear to influence smell function |
| Fasunla *et al*[6], 2012 | 16 GPA patients | No correlation between kidney involvement and smell function. GPA patients with and without past history of sinonasal operations did not show any significant difference in sense of smell |
| Proft *et al*[8], 2014 | 44 GPA patients | GPA patients with elevated CRP values showed lower scores from smell tests. GPA patients with a higher extent of damage showed a tendency for reduced scores only for the threshold, but not for the identification, the discrimination or the total score (TDI score). No correlation between kidney involvement and smell function. GPA patients under therapy with azathioprine showed significantly lower scores only for odour discrimination. GPA patients undergoing low-dose GC therapy showed a tendency for lower thresholds scores compared to patients without GC therapy |
| Tallab *et al*[12], 2014 | 1 EGPA patient | Subjective improvement of smell function after immunosuppressive therapy |

GPA: Granulomatosis with polyangiitis; EGPA: Eosinophilic granulomatosis with polyangiitis; CRP: C-reactive protein; GC: Glucocorticoids.