Pathological Findings of Post-Viral Olfactory Dysfunction: A Systematic Review

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Abstract

The coronavirus disease 2019 pandemic has shed light on the post-viral olfactory dysfunction (PVOD). Post-viral olfactory dysfunction is temporary for most people and usually subsides when the common cold symptoms ameliorate. However, in some patients, this condition can persist for several weeks or months. The exact pathological mechanisms of persistent olfactory loss secondary to upper respiratory tract infection (URTI) is unknown, and there is a lack of effective treatment. An increased understanding of pathology could possibly translate into new therapeutic regimens. The aim of this systematic review is to synthesize primary data regarding histopathological and neuropathological findings in patients with PVOD secondary to URTI. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines was followed. Databases PubMed and Web of Science were searched with keywords and mesh terms to identify relevant articles. The quality of included studies was assessed with the Newcastle–Ottawa Scale for observational studies. The search yielded a total of 847 articles, after excluding duplicates and articles that were not relevant. A total of 12 studies were selected. The main findings of this review were: olfactory bulb (OB) volume was decreased in patients with PVOD, there was a negative correlation between OB volume and duration of olfactory loss, both primary and secondary olfactory cortex changes were found in terms of structure and functionality, and the olfactory sensory neurons and nerve bundles were reduced in patients with PVOD. The mechanisms of PVOD are complex. This review found that viral URTI is attributable to structural and functional changes at multiple locations of the olfactory system.

Keywords: Anosmia, olfactory bulb, olfactory cortex, olfactory dysfunction, post-viral, URTI

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has shed light on the importance of olfactory dysfunction (OD) and has increased the awareness of this condition among the general population and physicians. Recent reports indicate that the incidence rate of OD in COVID-19 varies between 33-68%.[1] An intact sense of smell is important for various domains in life like nutrition intake and avoiding hazardous smoke or gas. Furthermore, OD has been associated with a reduced quality of life.[2] Before the COVID-19 pandemic, OD secondary to viral upper respiratory tract infection (URTI), termed post-viral OD (PVOD), was often overlooked by physicians.[3] Unfortunately, there is no effective treatment for this condition and since approximately 5% of the general population is believed to be affected by OD secondary to various etiologies including post viral.[3] This is a condition that requires more attention and research. Post-viral OD has been a well-known clinical problem to otorhinolaryngologists for a long time[4] and is one of the most common causes of OD.[5] However, the pathophysiological mechanisms of PVOD are poorly understood. The olfactory system consists of several structural and functional cellular components that are important for normal olfactory function. For smell to be perceived, odorant molecules must bind to binding proteins in the olfactory mucosa. This odorant-protein complex then activates olfactory sensory neurons (OSN) that extend their axons through the cribriform and then synapse with mitral and tufted cells at the surface of the olfactory bulb (OB).[6] The OB is a neural structure that is located at the base of the frontal lobe and works as a relay station that receives information from OSN.[7] Finally, axons from secondary order neurons converge and form the olfactory tract (cranial nerve 1), which projects to specific brain areas that process olfactory information, mainly the primary and secondary olfactory cortex.[6] Additionally, there are multiple supporting cells and regenerative cells of the olfactory mucosa that are important for normal olfactory function.[8]

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In the acute phase of a viral URTI, OD is known to be caused by swelling and edema of the nasal mucous membrane. This temporary smell loss subsides in most patients when the symptoms of the URTI ameliorate. However in some patients, the resolution is incomplete and the OD can persist for a long time.[9] The cause of this is unclear, but destruction of OSNs in the olfactory mucosa has been suggested.[10] Animal studies have also shown destruction of central olfactory pathways after inoculation of different viruses.[11,12]

There are several viruses known to cause URTI in humans, the most common are rhinovirus, parainfluenza, coronavirus, and Epstein–Barr virus.[13]

The aim of this review is to summarize and synthesize the current primary literature that reports histopathological and neuropathological changes of the olfactory pathway secondary to viral URTI in patients with PVOD. Olfactory pathway units (units of interest are the olfactory epithelium (OE), OSN, OB, or olfactory cortex). A better understanding of the pathology of PVOD could possibly translate into more new effective therapies in the future.

MATERIALS AND METHODS

Inclusion and Exclusion Criteria

Primary literature that investigated histopathological or neuropathological findings in patients with PVOD secondary to viral URTI was included. Studies not describing OE, OB, or olfactory cortex were excluded, COVID-19 studies, studies assessing PVOD prognosis or treatment, non-English articles, studies not available in full text, case studies, reviews and meta-analyses, commentaries and editorials, animal studies, and OD secondary to non-viral causes. There were no exclusion criteria regarding publication date.

Search Strategy

To maximize the number of results, the following blocks; (1), (2), and (3) were combined with the Boolean operator "AND." Each block included both mesh-terms and keywords and was combined with the Boolean operator "OR." Each block is listed below.

Block 1:

- "Respiratory Syncytial Virus Infections," "Respiratory Syncytial Viruses," "Cytomegalovirus Infections," "Muromegalovirus," "Cytomegalovirus," "Encephalitis, Herpes Simplex," "Herpesvirus 1, Human," "Herpes Simplex," "Orthomyxoviridae Infections," "Influenza A virus," "Coronavirus Infections," "Coronavirus," "SARS Virus," "Severe Acute Respiratory Syndrome," "Paramyxoviridae Infections," "Respiratory Tract Infections," "adenovirus infections, human," "adenoviruses, human," "Rhinovirus," "Common Cold," "Respiratory syncytial virus," "Cytomegalovirus," "herpes simplex encephalitis," "herpes simplex virus," "Herpes simplex type 1 virus," "herpes simplex," "Epstein-barr virus," "influenza virus," influenza, "influenza A virus," coronavirus, "severe acute respiratory syndrome," SARS, "parainfluenza virus," adenovirus, rhinovirus, Virus, Viral, Postviral, "post-viral," "postinfectious," postinfectious, URI, URTI.

Block 2:

- "Olfaction disorders," Anosmia, "Olfactory dysfunction," "olfactory disorder," "smell disorder," "smell dysfunction," "smell impairment," "impaired olfaction,""olfactory loss,""olfactory deficit,""smell blind," dysosmia, parosmia, "Loss of Smell,""Smell Loss," Smell, Hyposmia.

Block 3:

- "Olfactory Bulb," "Olfactory Mucosa," "Olfactory Pathways," "Olfactory Receptor Neurons," "Olfactory Nerve," "Olfactory bulb," "olfactory mucosa," "olfactory pathway," "olfactory receptor neuron," "olfactory epithelium,""olfactory neuron,""nasal mucosa."
- "pathogenesis," "sustentacular cells," "neuropathology," "mitral cell," "Histopathology," "olfactory route," "olfactory sensory neuron," pathogenicity, pathogenic, cytopathology, morphology, pathophysiology, "olfactory cortex," morphology, "olfactory neuroepithelium."

Search Process

The Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines[14] were followed for this systematic review. The final search was conducted on October 19, 2022, in the databases PubMed and Web of Science from inception through October 19, 2022, for primary studies reporting pathological findings in the olfactory system of patients with PVOD. The search combined Medical Subject Headings (MeSH terms) and keywords. Some of the keywords have been truncated to find alternative endings. In Web of Science, there is no controlled vocabulary; hence the MeSH terms stated in "Search terms" could not be applied for this search. For this reason, the MeSH terms were excluded for the search in Web of Science. The final search results were limited to the English language only.

The search process started with searching for each individual block (1-3) that is stated in "Search words" in both PubMed and Web of Science. Then block 1, 2, and 3 were combined. Duplicates were removed using the software program "Zotero" (v. 6.0.18, Digital Scholar). The authors reviewed titles and abstracts of articles found in the original search and excluded articles that did not meet inclusion criteria. The final search resulted in a total of 12 articles that were deemed to be of relevance. On October 21, 2022, reference lists of selected articles were reviewed but no additional studies were found.

Evaluation of Quality

The quality of the included case–control and cohort studies was evaluated using the Newcastle–Ottawa scale[15] in terms of selection, comparability, and exposure. A modified version of the Newcastle–Ottawa scale was used for studies with a cross-sectional design.[16] The study's quality was considered low, moderate, or high quality when points were 3 or less, 4-5, or 6 and above, respectively, in the Newcastle–Ottawa scale.

Data Collection

Data extraction was completed by the first author. The following data were extracted from the studies investigating neuropathologic findings;

Main Points

- *Covid-19 pandemic has shed light on the post-viral olfactory dysfunction (PVOD).*
- *PVOD is temporary and usually subsides when the common cold symptoms ameliorate. However, in some patients this condition can persists for several weeks or months. The exact pathological mechanisms of persistent olfactory loss secondary to upper respiratory tract infection (URTI) is unknown and there is a lack of effective treatment.*
- *Viral URTI is attributable to structural and functional changes at multiple locations of the olfactory system.*
- *There is a negative correlation between olfactory bulb volume and duration of olfactory loss.*
- *The mechanisms of PVOD are complex. An increased understanding of pathology could possibly translate into new therapeutic regimens.*

authors and publication date, study design, country, sample size, mean age of study participants, imaging modality, olfactory function test used, anatomical site or brain region studied, and a summary of the results. The following data for histopathological studies were collected; authors and publication date, study design, country, sample size, anatomical site studied, and a summary of the results.

Ethical Considerations

No ethical approval was needed for this systematic review since it is a review of studies already performed. Seven studies included in this review clearly stated that they had been ethically approved by committees or review boards.[17-23] Four studies clearly stated they followed the accordance of the Declaration of Helsinki.[17,18,20,24] Four studies did not clearly state that their studies have been ethically approved or followed specific guidelines.[9,25-27] Six studies did not clearly state written or informed consent.[9,19,24-27]

RESULTS

Literature Search

In total, 1247 articles were identified by searching in the databases PubMed and Web of Science. In PubMed, 737 articles were found and 509 articles were found in the Web of Science. A total of 399 duplicates were excluded. This left 847 articles with title and abstracts that were reviewed independently by the first author. After screening titles and abstracts, 829 articles were excluded based on the following exclusion criteria: PVOD not addressed, animal studies, only PVOD diagnosis or treatment addressed, reviews. Thus, only 19 articles seemed relevant based on title and abstract for the current review. One article was excluded as it could not be retrieved in full text. The remaining 18 articles were obtained in full text, 6 of these were excluded from the final analysis as shown in Figure 1. No additional articles were found when screening the articles reference lists. Thus, a total of 12 studies were included in the final qualitative synthesis. Detailed information on the process of selecting articles is illustrated in Figure 1. Two studies were of high quality, 5 were of medium quality, and 5 were of low quality according to the results from the quality assessment, as seen in Tables 1-3.

Study Characteristics

A total of 12 studies met inclusion criteria for qualitative analysis. The studies were conducted in Türkiye, US, UK, Korea, Austria, Belgium, and Germany. Study characteristics and a summary of results for each study are described in Tables 4 and 5.

The included studies differed in design, methodology, and outcomes. All included studies had an observational design. A subtotal of 7 studies followed a cross-sectional study design, 4 were case–control studies, and 1 had a retrospective cohort design. The included studies involved

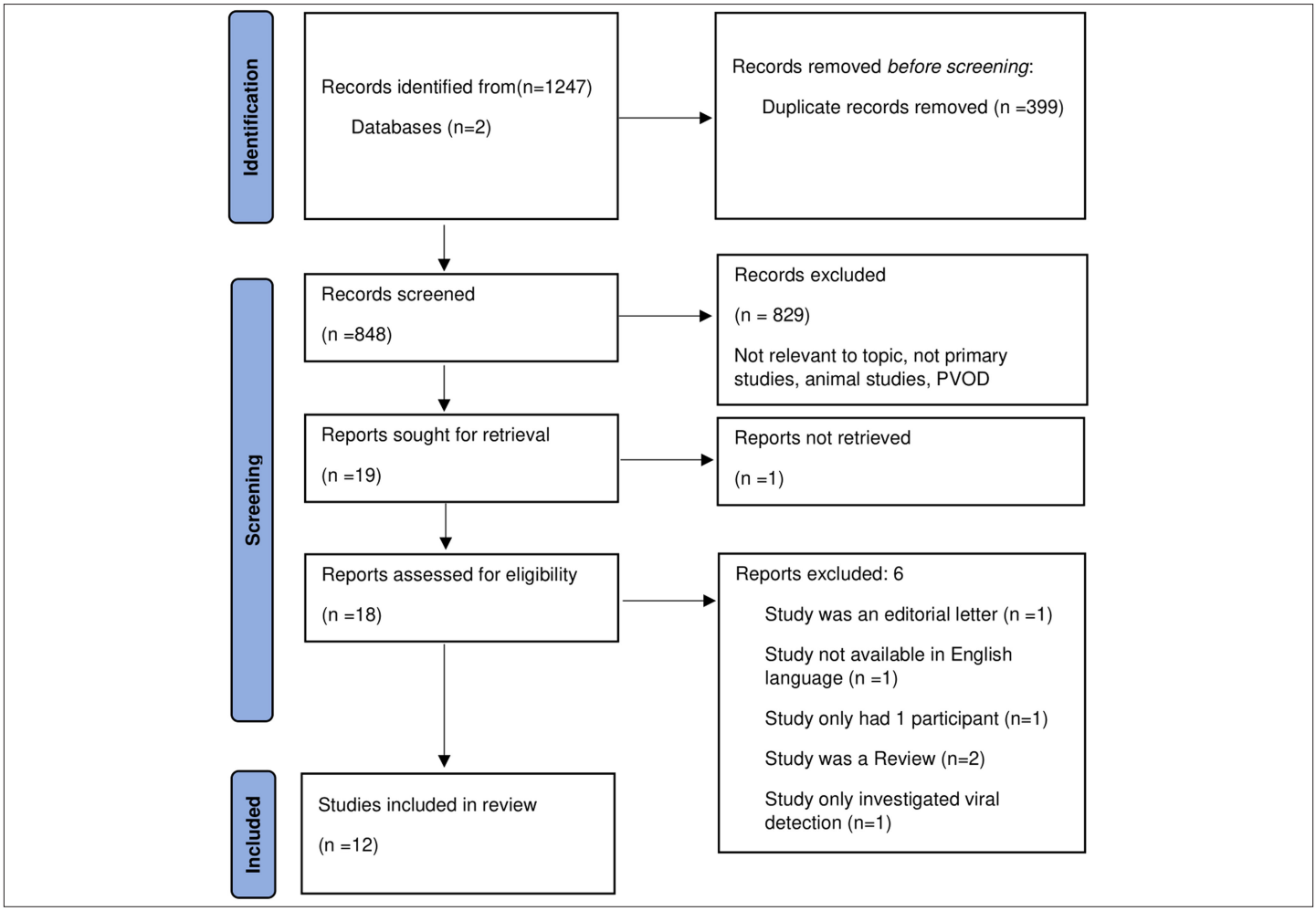

Figure 1. Process of selecting the articles. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart.

Table 1. Evaluation of Quality Regarding Rrisk of Bias for Cross-Sectional Studies with a Modified Version of the Newcastle–Ottawa Scale. Low quality = 3 or less, medium quality = 4-6, high quality = 7, or more. Maximum total score is 9

		Selection				Comparability	Outcome		
Author	Study Design	Representative Sample?	Sample Size Adequate	Non-respond ents	Ascertainment of Exposure	Based on Design or Analysis	Assessment of Outcome	Statistical Test	Total Score
Kim et al[19]	Cross- sectional	–	–	–	++	++	++	+	7
Wolf et al[20)]	Cross- sectional	–	–	–	++	–	–	+	3
Yao et al[21]	Cross- sectional	–	–	–	++	++	++	+	7
Romba ux et al[25]	Cross- sectional	–	–	–	++	–	++	+	5
Yamag ishi et al[26]	Cross- sectional	–	+	–	++	–	–	–	3
Yamagishi et al[27]	Cross- sectional	–	–	–	++	–	++	–	4
Jafek et al[9]	Cross- sectional	–	–	–	++	–	++	–	4

Table 2. Evaluation of Quality regarding Risk of bias for Case-control studies with the Newcastle–Ottawa scale. Low quality = 3 or less, Medium Quality = 4-6, High Quality = 7 or more. Maximum Total Score is 9

		Selection				Comparability	Exposure			
Author	Study Design	Case Definition Adequate?	Case Representative?	Selection of Controls	Definition of Controls	Based on Design or Analysis	Ascertainment of Exposure	Same Method for Cases and Controls	Non- Response Rate	Total Score
Yildiri m et al[23]	Case–control	+	+	–	–	++	–	+	–	5
Altundag et al[18]	Case– control	+	–	–	–	–	–	+	+	3
Altundag et al[17]	Case– control	+	–	–	–	++	–	+	+	5
Mueller et al[24]	Case– control	–	–	–	–	–	+	+	–	2

Table 3. Evaluation of Quality Regarding Risk of Bias for Retrospective Cohort Studies with the Newcastle–Ottawa Scale. Low Quality = 3 or Less, Medium Quality = 4-6, High Quality = 7 or More. Maximum Total Score is 9

		Selection				Comparability	Exposure			
Author	Study Design	Representative Sample?	Selection of Non-Exposed	Ascertainment of Exposure	Demonsration of Outcome	Based on Design or Analysis	Ascertainment of Outcome	Follow-Up	Adequacy of Follow-Up	Total Score
Yildirim et al[22]	Retrospective Cohort	–	–	+	–	–	–	+	+	3

Table 4. Summary of Included Articles that Investigated Neuropathologic Findings in Post-Viral Olfactory dysfunction

Author and Year	Study Design	Country	Sample Size	Mean Age	Imaging Technique	Test Used to Evaluate Oolfactory Function	Anatomical Site Studied	Summary of Results
Yildirim et al (2021)[22]	Retrospective cohort	Türkiye	N = 97	45.9	MRI and DTI	Sniffin sticks	OB and olfactory tract	Decreased OB volume, deformed morphology, and increased SI.
Yildirim et al (2020)[23]	Prospective cohort	Türkiye	N = 106	47	CT + MRI	Sniffin sticks	OB and olfactory tract	No significant decrease in OB volume. Deformed OB and tract morphology.
Kim et al. (2012)[19]	Cross-sectional	Korea	N = 18	57	FDG-PET	Korean version of Sniffin sticks	Primary and secondary olfactory cortex	Decreased metabolic activity in the primary and secondary olfactory cortex.
Altundag et al. (2021)[17]	Retrospective cohort	Türkiye	N = 91	43.7	MRI and CT	Sniffin sticks	OC	Increased width and volume of OC and increased SI.
Wolf et al. (2018)[20]	Cross-sectional	Austria	N = 21	56	N/A	Sniffin sticks	OC proteome	No proteins significantly altered.
Rombaux et al. (2006)[25]	Cross-sectional	Belgium	N = 26	46	MRI	Sniffin sticks	OB	Reduced OB volume. A negative correlation between OB volume and olfactory function.
Mueller et al. (2005)[24]	Cross-sectional	Germany	N = 22	57	MRI	Sniffin sticks	OB	Decreased OB volume.
Altundag et al. (2021)[18]	Retrospective case–control	Türkiye	N = 71	47.4	CT	Sniffin sticks	OC	Increased OC width and volume compared to controls.
Yao et al (2018)[21]	Cross-sectional	UK	N = 38	37.7	Voxelbased MRI	T & T olfactometry and Sniffin sticks test	OB and OFC	Significant decrease in gray matter volume of OFC and decreased OB volume.

CT, computed tomography; FDG-PET, fluorodeoxyglucose-positron emission tomography; MRI, magnetic resonance imaging; OB, olfactory bulb; OC, olfactory cleft; OFC, orbitofrontal cortex; SI, signal intensity, T & T, odor-threshold & identification.

Table 5. Summary of Articles that Investigated Histopathologic Findings in Post-Viral Olfactory dysfunction Patients

Author and Year	Study Design	Country	Sample Size	Test Used	Region Studied	Summary of Results
Yamagishi et al (1994)[26]	Cross-sectional	Japan	N = 70	T & T olfactometry and Alinamin injection test	OE	Reduced number of OSN and nerve bundles
Yamagishi et al (1990)[27]	Cross-sectional	Japan	N = 10	Data were missing	OE	Decreased number of OSN and atrophy of OE
Jafek et al (1990)[9]	Cross-sectional	US	N = 17	Several different tests used	OE	Degeneration of ciliated OSN

OE, olfactory epithelium; OSN, olfactory sensory neurons; T & T, odor-threshold & identification.

a total of 587 patients with PVOD. Data from a subtotal of 490 patients were collected from the studies investigating neuropathological findings. Data from a subtotal of 97 patients were collected from studies examining biopsy material. The mean age of participants ranged from 38 to 57 years. Mean disease duration ranged from 1 month to 9 years. Two studies[9,27] lacked data regarding the age of the study participants.

There was a great variability in how PVOD was diagnosed across the studies. Most of the studies diagnosed PVOD based on patient history, objective measurement of olfactory function, and clinical examination. Olfactory function was measured objectively with different tests in all studies except for 1 study.[27] The most used test across the studies was the Sniffin' sticks test, which was used in all studies except 3 studies.[9,19,21] Kim et al[19] used a Korean version of the Sniffin' sticks test to objectively measure olfactory function. Yao et al[21] used the Toyoda and Takagi's olfactometry test in addition to the Sniffin' sticks test, and Jafek et al[9] used the University of Pennsylvania Smell Identification test. The details of these tests have been described in other studies.[28-30] Yamagishi et al[27] did not describe how olfactory function of their study subjects was evaluated.

Different imaging modalities were used across the included studies to assess structural and functional changes in different units of the olfactory

pathway. Magnetic resonance imaging (MRI) was used to assess the OB volume in 5 studies.[21-25] The morphology and signal intensity of the OB and olfactory nerve tract were assessed with MRI in 2 of these studies.[22,23] Voxel-based MRI (VBM-MRI) was used by Yao et al[21] to evaluate gray matter volume in the primary and secondary olfactory cortex of patients with PVOD. Two studies[17,18] evaluated computed tomography images of the olfactory cleft (OC) width and total volume. Fluorodeoxyglucose-positron emission tomography was used in 1 study[19] to assess metabolic activity in the primary and secondary olfactory cortex. Due to great variation in design, methodology, and outcome measured, a meta-analysis could not be performed.

Regarding the biopsy studies,[9,26,27] immunohistochemical staining and electron microscopy were utilized across all studies to evaluate residual cells of olfactory mucosa of patients with PVOD. Yamagishi et al[26] used hematoxylin–eosin (H & E) staining in addition to immunohistochemical staining.

Neuropathologic Findings

Five studies[21-25] assessed the OB volume. All of these studies except 1[22] found that the OB volume was decreased in patients with PVOD. Yao et al,[21] Yildirim et al,[23] and Rombaux et al[25] also found a negative correlation between OB volume and the duration of olfactory loss. Two studies[22,23] also investigated the morphology and signal intensity of the OB and olfactory tract in patients with PVOD and found that the OB and olfactory tract had a deformed morphology and abnormally increased signal intensity. In addition to measuring OB volume, Yao et al[21] also investigated the gray matter volume in the olfactory cortex and found that patients with PVOD had significantly smaller right OFC volume compared to controls. They also found a negative correlation between right OFC volume and the duration of OD. Two studies[17,18] measured the OC width and total volume and found that both width and total volume were increased in patients with PVOD compared to controls, and this finding was considered a risk factor for PVOD. Kim et al[19] investigated the metabolic activity in the primary and secondary olfactory cortex of patients with PVOD. They found that the metabolic activity was decreased in the following cortical areas: right piriform gyrus and parahippocampus (areas of the primary olfactory cortex) and bilateral insular cortices and medial and lateral temporal cortex (areas of the secondary olfactory cortex). Wolf et al[20] investigated the proteome of the OC in patients with PVOD and found a total of 1177 different proteins in the OC, but none of these were significantly altered compared to controls.

Histopathological Findings

Three studies[9,26,27] investigated histological changes of the olfactory epithelium (OE) in biopsies taken from patients with PVOD. Jafek et al[9] investigated ultrastructural changes of the OE in patients with anosmia and hyposmia secondary to viral URTI. They found that the OE was disorganized and that the numbers of OSN were greatly reduced in patients with anosmia. In the patients with hyposmia, the OSN was also reduced but not to the same extent as in patients with anosmia. Basal cells and supporting cells of the OE appeared normal across all 3 histological studies. Yamagishi et al[26] investigated specimens obtained from 70 patients with PVOD using H & E-staining and immunostaining prior to electron microscope observations. They found that OSN and nerve bundles were reduced in most samples, and there was variable degeneration of the OE across the samples. Yamagishi et al[27] investigated histological changes with immunostaining prior to electron microscope observations in 3 patients with smell loss following a common cold. They found that patients with PVOD had a reduced number of OSN and nerve bundles.

DISCUSSION

The pathogenesis of PVOD is poorly understood but both peripheral and central causes of PVOD have been proposed. Potential mechanisms include damage to the cells of the OE, OB, or olfactory cortex secondary to direct viral damage or inflammation. Damage to supporting cells and basal cells of the OE impeding regeneration has also been suggested as a potential mechanism of persistent PVOD.[9] Jafek et al[9] reported greatly reduced numbers of OSN in patients with anosmia and to a lesser extent in patients with hyposmia. Hence, a correlation between the extent of reduction of OSN and olfactory function could be made. Olfactory epithelium consists of several different cell types, but one of the most important is the OSN that is the first step in transducing and relaying olfactory information.[31] This review consistently reports that patients with PVOD had a reduced numbers of OSN and nerve bundles,[9,27,32] which supports the hypothesis of peripheral damage as the main cause of PVOD. The biopsy studies included in this review did not find any evidence of damage or alteration to the basal cells or supporting cells in samples taken from patients with PVOD.

The second step in processing olfactory information occurs at the OB, which receives information from the OSN and forwards this information to different regions of the olfactory cortex.[33,34] This review consistently revealed that OB volume is decreased in patients with PVOD. A total of 5 studies in this review[21-25] investigated the OB volume in patients with PVOD and revealed a decreased OB volume compared to healthy controls, except 1 study,[22] which could be due to the small sample size of the study. This finding is consistent with previous studies that have shown decreased OB volumes in patients with OD secondary to neurodegenerative disease and traumatic brain injury.[35,36] However, since the included biopsy studies revealed a reduced number of OSNs, and the absence of sensory input has been shown to cause brain remodelling,[37] it is unclear if the OB volume reduction in the aforementioned studies is the effect of direct viral damage or the cause of diminished sensory input. Diminished sensory input is, however, the most likely explanation since OB volume is believed to be indicative of the average number of OSNs in the OE.[38] Furthermore, 3 of the studies included in this review[21,23,25] found a negative correlation between OB volume and the duration of olfactory loss, which is considered a feature of peripheral damage.[25] However, animal studies have shown that some viruses can cause damage to central olfactory pathways.[39,40] In addition, Mori et al[41] have shown that parainfluenza virus can infect OSNs and establish long-term persistence in the OB of mice, potentially causing direct damage to the OB. The piriform cortex, which is part of the primary olfactory cortex, is directly connected to the extracorporeal environment through the olfactory nerve,[42] and this part of the central nervous system (CNS) is the most likely to be affected in PVOD.

Only 2 studies included in this review investigated functional and structural changes in central cortical areas related to olfaction.[19,21] Kim et al[19] is the only study to date that have investigated metabolic activity in CNS of patients with PVOD and found decreased metabolic activity in both primary and secondary olfactory cortex, including the piriform cortex. However, since this is the only study investigating metabolic activity with small sample size, it is difficult to draw conclusions from studies outcomes. Furthermore, this study cannot discriminate between peripheral and

central mechanisms of PVOD. It is possible that the changes seen in the CNS were the consequence of reduced sensory input causing decreased metabolic activity.

Two of the studies that evaluated the OB volume in patients with PVOD also investigated signal intensity (SI) and morphology of the vital components of the central olfactory system i.e OB, olfactory tract, and OC.[22,23] SI is an indicator of edema and inflammation, and a deformed morphology is a sign of inflammation and attempted regeneration. These 2 studies found abnormally increased SI and deformed morphology of both the OB and olfactory tract. This finding supports the hypothesis that viral infection may also cause direct damage to central olfactory pathways.

The quality assessment of studies in this review found that 2 studies[19,21] were of high quality, 5 studies[9,17,23,25,27] were of medium quality, and 5 studies[18,20,22,24,26] were of low quality. The 4 studies that showed a reduction of the OB volume in patients with PVOD included 1 study of high quality,[21]2 of medium quality[23,25] and 1 study[24] of low quality. This means that there is a risk of bias across these studies; therefore, the findings of the studies should be interpreted with caution. Furthermore, the histological studies that found evidence of reduced OSN and nerve bundles were of moderate-to-low quality; none were of high quality. Additionally, the sample size in these studies was small, and therefore it is difficult to draw conclusions from the findings. A major weakness of this review is that most included studies had a small sample size and followed a cross-sectional study design. Thus, it was not possible to differentiate between peripheral and central causes of PVOD.

Also, the duration between onsets of olfactory loss and imaging evaluation was varying from 1 month to 9 years across all studies. This variation in disease duration makes it more difficult to make conclusions. It is possible that including studies with both long and short disease durations may have influenced the material in some way. It is possible that including only patients within a predefined disease duration interval would have made the results different and easier to generalize to PVOD patients with similar disease duration.

Another issue is that the mean age of patients differed across the studies, and since there is evidence of OB volume reduction with increased age,[43] the decrease in OB volume seen in some of the included studies in this review with older study populations could partly be due to normal aging. However, studies that investigated the OB volume[21,23,25] age-matched with a healthy control group, so this possibility is not likely.

Finally, only 2 databases were searched to identify relevant articles; due to this small set of databases, some relevant articles may have been missed.

CONCLUSION

The main findings of this review were that the OB volume was decreased in patients with PVOD and that OSN and nerve bundles were reduced in the olfactory mucosa. A negative correlation between OB volume and disease duration was also found, supporting the hypothesis of peripheral damage. However, since few number of studies of varying quality were included in this review, these results should be interpreted with caution.

Peer-Review: Externally peer-reviewed.

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