REVIEW ARTICLE

CONTENTS

COVID-19 associated anosmia in pediatric patients: subject publications review

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ABSTRACT

Aim: To review the publications subject to the problem of COVID-19 associated anosmia incidence in pediatric patients as well as its pathogenesis, diagnostics, treatment and recovery. The peculiarity of pediatric COVID-19 anosmia is due to children accounting for very low percentage of COVID-19 patients (comparing to one in adults), mostly with milder course of the disease. Awareness of anosmia and its proper diagnostics is crucial in children and adolescents, considering it can be the only manifestation in COVID-19 positive pediatric patients.

Materials and Methods: In order to achieve this goal a meta-analysis of information from databases followed by statistical processing and generalisation of the obtained data was carried out.

Conclusions: Publications on COVID-19 anosmia in children and adolescents are less numerous than those concerning adult patients, so it is important to use every single trustworthy one. Anosmia/ageusia may be the only symptom, early identifier and the strongest predictor of COVID-19 infection in pediatric patients. Prospects for further scientific researches. Further researches regarding differential diagnostics of COVID-19 and other infections, including seasonal influenza, manifesting with both olfactory and taste dysfunction as well as anosmia diagnostics in children and adolescents with autistic spectrum and different types of mental disorders are possible.

KEY WORDS: COVID-19 infection, olfaction, anosmia, hyposmia, ageusia

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INTRODUCTION

On March 11, 2020, the World Health Organization (WHO) assessed that COVID-19 outbreak could be described as a pandemic due to the alarming levels of spread and severity. In April 2020, WHO included loss of smell (anosmia) and loss of taste (ageusia) into the official list of common COVID-19 symptoms. The statistics in COVID-19 positive children and adolescents show that loss of smell and taste are common symptoms not only in adults but in pediatric patients as well and may even be the only presentation of the abovementioned infection.

AIM

The objective of the study is to review the publications subject to the problem of COVID-19 associated anosmia incidence in pediatric patients as well as its pathogenesis, diagnostics, treatment and recovery. The peculiarity of pediatric COVID-19 anosmia is due to children accounting for very low percentage of COVID-19 patients (comparing to one in adults), mostly with milder course of the disease. Awareness of anosmia and its proper diagnostics is crucial in children and adolescents, considering it can be the only manifestation in COVID-19 positive pediatric patients. That is why studying the trustworthy subject resources plays an important part in professional experience exchange for earlier detection of the disease and prevention of its further spread.

MATERIALS AND METHODS

In order to achieve this goal a meta-analysis of information from databases followed by statistical processing and generalisation of the obtained data was carried out

REVIEW AND DISCUSSION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a highly infective virus spread around the world that affects a considerable number of people [1]. Adults appear to play a key role in spread of the virus

in families. Transmission from a household member, often showing symptoms before them, accounted for the majority of children for whom the source of infection was identified [2, 3]. Despite this impetuous spread, the prevalence of Severe Acute Respiratory Syndrome Coronavirus 2 in children ranges from 1-5% that is very low as compared to the total infected population [4]. Difficulty in clinical diagnostics of the disease in children due to their inability to explain their symptoms often leads to overlooking this disease. Besides, new modes of presentation, in addition to the classical telltale signs, are being reported. In this scenario, health professionals who deal with the children should be familiar with different modes of presentation of this disease in the pediatric population [1]. Nevertheless, since the initial stages of the coronavirus disease 2019 (COVID-19) pandemic, the number of infected children has grown significantly. This may be because the testing criteria for SARS-CoV-2 have changed as exposure risks, COVID-19 associated symptoms, laboratory testing capacity and priority populations evolved during the pandemic [5].

At the early stage of the pandemic, COVID-19 was primarily considered a pulmonary disease with extrapulmonary manifestations. Currently, data support that SARS-CoV-2 infection is a systemic disease with pulmonary involvement. The most frequent non-pulmonary manifestations in children were symptoms from gastrointestinal system, renal system, cardiovascular system, neurological system, lymphatic system, cutane, hepatic system, visual, gustatory and olfactory analyzers [6].

Despite children and adolescents being more susceptible to certain infectious diseases because of their developing immune system [7], COVID-19 usually has a relatively mild course in pediatric population [2, 8, 9]. Even though severe illness and death may occur [10], children and adolescents still have better incomes and lower mortality rates than adults do [11]. In children who test positive for SARS-CoV-2, the most common symptoms are anosmia and dysgeusia, nausea/vomiting and headaches in outpatients and fever in hospitalized children [11,12]. Clinical symptoms in children are not pronounced, rendering it difficult to make a diagnosis at the outset [13], among other things due to overlap with symptoms of common respiratory and gastrointestinal tract infections including abdominal pain and diarrhoea, nausea, vomiting [2, 10]. Some pediatric patients may present as asymptomatic and thus easily be missed [2].

ENT symptoms in children with SARS-CoV-2 are not specific [1]. In adults, the neck and head may be affected to varying degrees, the main symptoms being changes in taste and smell. In pediatric practice, nasal respiratory and olfactory functions are affected in different ways and various dyspeptic disorders as well as conjunctivitis and dermatitis may be associated with them [13]. In children with COVID-19, anosmia may be unaccompanied by discomfort in other organs and systems, unlike in adults [14]. Anosmia was found to be a significant predictor of a positive COVID-19 test result with positive COVID-19 reported by 75% of patients with anosmia [10]. Smell disorders (hyposmia, anosmia) occur among 15-20·% of the general population [15]. The term anosmia means complete loss of the ability to smell. In the daily clinical work, anosmia is the term used to describe the inability to smell oneself or one's surroundings. Fragments of olfaction (sense of smell) may be preserved but are generally useless in a social context. The prevalence of anosmia is 2-5% [15, 16,17]. Loss of olfactory input has several consequences: we no longer receive information about potential hazards such as smoke, fire, leakage of chemicals and poisonous substances, as well as spoiled food, leading to anxiety and stressful alertness. In addition, the smell of food is absent or distorted to such a degree that sufferers are unable to prepare and enjoy a meal. In one-third of patients, this hedonic loss gives rise to depression [17, 18]. In many cases, the patient's primary complaint is loss of taste (ageusia). The underlying mechanism is that the sense of smell adds all the subtle elements of taste beyond sour, salt, sweet, and bitter. As clinicians, we should be very aware of anosmic symptoms [19].

Postviral anosmia and chronic rhinosinusitis are two common causes of anosmia, with their pathophysiology largely being conductive, sensorineural or mixed [14]. Less common causes include nasal polyps, tumors, head trauma, chemotherapy or radiotherapy and drug-induced anosmia such as that due to tricyclic antidepressants or antipsychotics. Anosmia may recover after relief of nasal obstruction and inflammation, in addition to self-regeneration of olfactory neurons through stem cells in the olfactory neuroepithelium [14].

Smell dysfunction is known to be common in viral infections. Several viruses can cause loss of smell via inflammatory reaction in nasal mucosa, leading to rhinorrhea [19]. Common viruses associated with postviral anosmia include human coronaviruses and rhinoviruses. Edema and congestion of the nasal mucosa in the olfactory cleft causes obstruction of airflow through the nose, resulting in conductive olfactory loss. Most cases of anosmia are temporary with spontaneous recovery. Chronic rhinosinusitis may produce more prolonged anosmia or hyposmia, with predominant sensorineural inflammation and death of olfactory neurons [14]. Anosmia (and dysgeusia) can help to differentiate the diagnoses [20], as they differ significantly from the already

well-studied symptoms of reduced or lost sense of smell in patients with bacterial and viral (non-COVID-19 infection) rhinosinusitis or allergic rhinitis [21].

Higher smell or taste dysfunction rates were associated with being female, younger age, smaller sample size, patients in Asia, and with comorbidities [22].

Recent studies have shed light on the mechanisms that may underlie the loss of olfaction or gustation in COVID-19 patients [23]. SARS-CoV-2 has been found to replicate particularly well in the nose, with high viral loads detected there soon after symptom onset [32].

Angiotensin-converting enzyme 2 (ACE-2) was determined as the functional receptor for SARS-COV-2 and the organs having this receptor are targeted [24].

ACE-2 (the main host cell receptor of SARS-CoV-2) and transmembrane serine protease 2 (TMPRSS-2 a cell surface protease involved in SARS-CoV-2 cell entry) are highly expressed in a variety of olfactory epithelial cell types, raising the possibility that viral invasion of these cells may lead to anosmia [22, 25]. It has also been suggested that transcribiform viral spread and infection of more proximal elements of the olfactory pathway via central nervous system (CNS) ACE-2 receptors may also contribute to olfactory dysfunction [26]. Alternatively, it is possible that at least some of the olfactory dysfunction is conductive-secondary to nasal congestion, swelling, or inflammation preventing olfactory molecules from reaching the olfactory cleft-rather than sensorineural [27]. This may be particularly true in the subset of patients who showed improvement of their olfactory dysfunction on follow-up, although further research is needed. ACE-2 is also highly expressed on the oral mucosa and tongue, representing a potential mechanism for gustatory dysfunction [28].

As children account for less than 2% of identified cases of (COVID-19) [10], it is hypothesized that the lower risk among children is due to differential expression of angiotensin- converting enzyme 2 (ACE-2) [8]. Bunyavanich et al. conducted a retrospective examination of nasal epithelium from individuals aged 4 to 60 years during 2015-2018 [29]. The research team found age-dependent ACE2 gene expression in nasal epithelium. ACE-2 gene expression was lowest in younger children and increased with age. Linear regression with ACE-2 gene expression as the dependent variable and age group as the independent variable showed that compared with younger children, ACE-2 gene expression was significantly higher in older children, young adults and adults [29]. The same conclusion was made by Dong et al. That team also reported the reduced infection rates owing to the lower expression of ACE-2 receptors in the respiratory epithelium of the pediatric population [8].

The common feature of the patients in the researches of Concheiro-Guisan et al. and Hatipoglu et al. was that the smell and/or taste disorder developed without nasal symptoms such as nasal congestion, nasal obstruction or rhinorrhea (nasal discharge) [18, 30]. Besides, magnetic resonance interference performed on some of those patients showed no anomalies of the olfactory bulbs and tracts [30]. Given the difficulties in discriminating COVID-19 from other common pediatric upper respiratory tract infections, it is possible to use existing anosmia assessment tools alongside olfactory screening questions. These could be performed by parents or medical professionals, within primary or secondary care or even be administered remotely with instruction [17].

The "U-Sniff" is a valid and reliable method of testing olfaction in children and can be used internationally [31]. The "U-Sniff" test has been used in pediatric practice since the age of three. It is considered to be the most reliable test for detecting anosmia [12]. In Spain, for example, "Kradeo", a 7-odorant identification test, is used. The test is designed for the clinical assessment of olfaction based on the identification of familiar odorants, selected according to the cultural context and eating habits and including jasmine, mint, anise, vinegar, cinnamon, lemon and a neutral odor [18]. Reliable methods for diagnosing anosmia have been developed for children five years and older. There have been no systematic studies for children under three years of age [12]. In Japan, "Open Essence", which is a Japanese odor identification test using 12 different odor cards, is performed and it shows partially correct answers [32].

While scratch and sniff tests are widely validated and suitable for use, the unit price is likely prohibitive for mass screening. Future testing using limited panels of "child-friendly" odors, for example, mint or banana on felt-pen like dispensers and other existing multiuse tests would be suitable in a classroom setting [17]. Additionally, jellybean or 'candy smell test' have been successfully used in children: a sweet is sucked or chewed while the child blocks their nose, they then release their nose to smell the sweet's flavor, identifying one of four possible choices provided [33]. Other forms of gustatory screening using 'sweet, salty, sour and bitter' tastes or identifying sudden change in dietary preferences/altered taste could also be used [17]. The main problem is that symptoms related to taste and smell are so subjective that it is hard to assess them in pediatric age groups [34].

The visual analog scales (VAS) can be used to subjectively and easily evaluate taste and olfactory sensations [32]. In this method, the normal or usual olfactory and gustatory statuses are shown as 100%, and the current status is self-reported. In this case, we mainly used VAS

for the quantitative evaluation of olfactory and gustatory dysfunctions associated with COVID-19 over hospitalized duration to prevent nosocomial SARS-CoV-2 infection [32].

Olfaction assessment in children should combine different methods of evaluation, and not rely only on identification tasks [35]. Other assessments of olfaction sensation such as the Alinamin can also be used. The Alinamin test is performed by intravenous administration of propyl disulfide [36]. Latency, which is defined as the time between the initiation of injection and recognition of the odor (garlic smell), and duration, which is defined as the time between the recognition and disappearance of the odor, are measured. Furukawa et·al. showed that latency is influenced by olfactory acuity and duration depends on olfactory adaptation [36]. They have also reported that nonresponders to the Alinamin test had poor recovery [36], indicating that the Alinamin test can estimate the prognosis of olfaction.

Modern medicine is wary of the use of corticosteroids in the treatment of postcovid anosmia. The use of such general strengthening agents as vitamin A, zinc, omega 3 polyunsaturated fatty acids, olfactory training is recommended. If they are ineffective, two weeks after the disappearance of other symptoms of COVID-19 for anosmia, a course of topical steroids intranasally is prescribed [28].

There is a trend to quick recovery of olfactory function in children with COVID-19 [10]. The duration of olfactory and taste dysfunction varied from 2 to 15 days with anaverage of 5.7 days [37]. Olfaction and taste recover spontaneously within a few weeks, along with the resolution of other symptoms [37]. The overwhelming majority of patients have no subjective olfactory complaints by the end of the first month [38-40].

It is considered that the patients who neglect their anosmia spread the disease easily without knowing being infected, so that this symptom should be taken into consideration to detect the patients in early period [20].

To reduce the potential of person-to-person transmission, the public should be advised, if they show symptoms of new-onset anosmia or ageusia, to self-isolate and seek help from healthcare professionals. Healthcare workers attending patients with such symptoms should implement strict infection control and isolation measures to protect against COVID-19 infection in healthcare settings. Testing for SARS-CoV-2 infection is recommended for these patients [14]. The importance of anosmia should not be underestimated, as it may be the only discriminating symptom of COVID-19, so it can provide diagnostic and testing criteria for patients with no other clinical presentation to prompt early diagnostic testing in children, especially in older ones, and thereby prevent potential transmission [17, 34].

CONCLUSIONS

- Publications on COVID-19 anosmia in children and adolescents are less numerous than those concerning adult patients, so it is important to use every single trustworthy one.
- Anosmia/ageusia may be the only symptom, early identifier and the strongest predictor of COVID-19 infection in pediatric patients.
- Lower ACE-2 gene expression in nasal epithelium in children and adolescents compared to one in adults results in lower COVID-19 infection rates in pediatric population, especially in younger children.

Prospects for further scientific researches. Further researches regarding differential diagnostics of COVID-19 and other infections, including seasonal influenza, manifesting with both olfactory and taste dysfunction as well as anosmia diagnostics in children and adolescents with autistic spectrum and different types of mental disorders are possible.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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