© Borgis New Med 2023; 27(3): 93-98 DOI: https://doi.org/10.25121/NewMed.2023.27.3.93

**Joanna Olędzka[1], **Wiktoria Baczewska[2], *Tomasz Lis[3], Lidia Zawadzka-Głos[3]

Chronic suppurative otitis media in patient with velopharyngeal insufficiency and submucous cleft palate – case report

Przewlekłe ropne zapalenie ucha środkowego z wyciekiem u pacjenta z niewydolnością podniebienno-gardłową i podśluzówkowym rozszczepem podniebienia – opis przypadku

[1]Student Pediatric Otorhinolaryngology Scientific Research Group 'Otorhino', Department of Pediatric Otolaryngology, Medical University of Warsaw, Poland
[2]Student Audiological and Phoniatric Scientific Research Group, Department of Pediatric Otolaryngology, Medical University of Warsaw, Poland
[3]Department of Pediatric Otolaryngology, Medical University of Warsaw, Poland
Head of Department: Associate Professor Lidia Zawadzka-Głos, MD, PhD

Keywords

chronic suppurative otitis media, submucous cleft palate, velopharyngeal insufficiency, posterior pharyngeal flap surgery

Summary

Otitis media with effusion (OME), especially the chronic form, is one of the most frequent cause of hearing loss among children. It is characterized by the presence of non-purulent – serous or mucoid fluid in the middle ear space. It is usually diagnosed during the otoscopic examination and tympanometry. One of the most effective treatment for this condition is ventilation drainage of the middle ear. A side effect of ventilation tube placement may be a discharge from the ear, sometimes of bacterial etiology, which is usually successfully treated with antibiotics. OME is closely related to auditory tube function, and that is why the patients with comorbidities that affect it, are more prone to this disease. Thus, such defects as a cleft palate (CP) results in developmental abnormalities which cause Eustachian tube dysfunction and velopharyngeal insufficiency (VPI) that have impact on middle ear. In this article we present a case of a boy with bilateral chronic suppurative otitis media after ventilation tube placement, in whom the antibiotic therapy failures with recurring symptoms and in-depth diagnostics revealed that the reason for the ailments was the submucous CP with VPI.

Słowa kluczowe

przewlekłe ropne zapalenie ucha środkowego, podśluzówkowy rozszczep podniebienia, niewydolność podniebienno-gardłowa, operacja z użyciem płata z tylnej ściany gardła

Streszczenie

Wysiękowe zapalenie ucha środkowego (OME), szczególnie postać przewlekła, jest jedną z głównych przyczyn utraty słuchu wśród dzieci. Charakteryzuje się obecnością nieropnego, surowiczego lub śluzowego płynu w jamie bębenkowej. Diagnozowane jest zwykle podczas badania otoskopowego i tympanometrii. Jedną z najskuteczniejszych metod leczenia tego stanu jest drenaż wentylacyjny. Komplikacją po założeniu rurki tympanostomijnej może być wyciek z ucha, czasem o podłożu bakteryjnym, zwykle leczony skutecznie antybiotykoterapią. OME jest ściśle związane z dysfunkcją trąbki słuchowej, przez co pacjenci z dodatkowymi obciążeniami wpływającymi na nią są bardziej podatni na występowanie tego schorzenia. Zatem takie wady, jak rozszczep podniebienia (CP), niosący za sobą nieprawidłowości rozwojowe powodujące dysfunkcję trąbki słuchowej Eustachiusza oraz niewydolność podniebienno-gardłową (VPI), ma wpływ na ucho środkowe. W artykule opisano przypadek chłopca z obustronnym przewlekłym ropnym zapaleniem ucha środkowego po zabiegu drenażu wentylacyjnego, u którego przez niepowodzenia antybiotykoterapii i nawracające objawy oraz dzięki pogłębionej diagnostyce, powodem dolegliwości okazał się wrodzony podśluzówkowy CP z VPI.

** These authors contributed equally as co-firts authors.

Introduction

Otitis media with effusion (OME) is a condition attached to the middle ear mucosa with the formation and retention of secretions in the tympanic cavity. It coexists with impairment of the Eustachian tube and is one of the most well-known diseases among children and infants (1). The condition is often bilateral and is typically seen during upper respiratory tract infections. It can also lead to middle ear infections and conductive hearing loss. It usually resolves spontaneously without complications but may be also associated with recurrence rate up to 30-40%, where 5-10% of patients have chronic disease (2). Children with a cleft palate (CP) and other midface abnormalities are particularly prone to chronic OME (3).

About 30-35% of medical consultations for acute infections in the first 5 years of life are due to acute otitis media (AOM) (4), which usually requires antibiotic therapy (1). It is characterized by the presence of purulent fluid in the tympanic cavity together with signs and symptoms of an acute infection which is predominantly of bacterial etiology. The most common bacterial organisms causing otitis media are *Streptococcus pneumoniae*, followed by *Haemophilus influenzae* and *Moraxella catarrhalis* (5). The associated symptoms include: severe ear pain, a feeling of fullness in the ear and purulent discharge from the ear (6).

The effusion formed in the ear is most often leveled by the procedure of ventilation tube placement. This is a common procedure to remove residual fluid in the tympanic cavity. The anterior inferior quadrant of the tympanic membrane is considered to be the appropriate incision segment. Otorrhoea after ventilation tube placement is a common postoperative complication seen by otorhinolaryngologists. It can be chronic or recurrent in the form of inflammatory discharge. Purulent or mucous discharge occurs accidentally in about 12-30% immediately after insertion of the grommet (7). When the discharge is lasting ≥ 2 weeks, chronic suppurative otitis media (CSOM) may be diagnosed (8).

As we mentioned earlier, OME is often associated with CP – a congenital anomaly, where the roof of the mouth remains opened due to incomplete fusion during fetal development (9), which occurs between the 4th and 12th week of fetal life. A palate consists of three layers: nasal mucosa, muscles (on each side: levator veli palatini, tensor veli palatini, palatopharyngeus, palatoglossus and uvular muscle) and oral mucosa.

Submucous cleft palate (SMCP) is one of the forms of the cleft palate, where the palatal mucosa is intact, covering the defect of cleft muscles inside, thus it is not visible (10). It can manifest itself in an overt and latent form, which is particularly difficult to diagnose. Traditionally there are 3 signs of the overt CP – zona pellucida (a translucent line in the middle of the soft palate due to muscle separation), bifid uvula and lack of posterior nasal spine (11). The presence of SMCP often appears in children after removal of the adenoid in the form of the post-surgery hypernasality.

CP is a common malformation within the craniofacial area. In Europe, the combined birth prevalence of this defect is estimated to be around 1 per 700 live births and varies across different ethnic groups and geographic regions (12).

Patients with CP have Eustachian tube dysfunction, which is the cause of OME (13). The reason for that is that the muscles building the soft palate are weaker and in the wrong alignment, resulting in improper tube opening.

Another issue is velopharyngeal insufficiency (VPI) – dysfunction of the velopharyngeal sphincter, which occurs in up to 80% of SMCP patients (14). The proper functioning of the velopharyngeal sphincter consists in coordinated movements of the soft palate, lateral and posterior pharyngeal walls. In this condition, nasal regurgitation can be observed from birth. Besides that in the group of children who developed speech, hypernasality is most often observed.

VPI is often corrected surgically because conservative treatment is mostly unsatisfactory. One of the common surgical treatments besides double opposing z-palatoplasty and radical intravelar veloplasty – is a form of pharyngoplasty – a posterior pharyngeal flap (PPF) surgery. It is a procedure aimed at creating an anatomical connection between the posterior pharyngeal wall and the soft palate using the posterior pharyngeal lobe. Usually there is no need to perform it, especially when a child did not develop speech and hypernasality. However, there are exceptional circumstances for pharyngoplasty (15).

Below, we present the case of the patient with CSOM in consequence of the congenital VPI and SMCP.

Case report

The 3-year-old male child was admitted to the Department of Pediatric Otolaryngology of University Children Clinical Hospital in Warsaw due to chronic OME for the purpose of ventilation tube placement.

Patient was born via spontaneous vaginal delivery at 38 week of gestational age. The mother had two previous pregnancies and two previous births. The Apgar score in the first minute was 4, with 2480 g of body mass and 51 cm of body length (50 and 3 centiles, respectively; from the WHO centile charts). Immediately after birth, he was intubated and hospitalized for a month in the intensive care unit.

Besides right diaphragmatic hernia, found during prenatal ultrasound examination, the boy presented craniofacial abnormalities including high-arched palate, bowel obstruction, decreased muscle tone, cryptorchidism and epilepsy. The patient was suspected for SMCP because of nasal regurgitation observed from birth but it decreased with age and was not further diagnosed. Therefore, the patient required multi-specialty care. Due to diaphragmatic hernia, in the first week of life he underwent life-saving surgery of bringing the abdominal organs back from the thoracic

cavity and sewing in Gore-tex patch. Other procedures were laparotomic adhesions release (due to obstructed bowel) and bilateral orchidopexy, in the first and the seventeenth month of life, respectively.

Based on the whole clinical presentation, a genetic testing was conducted, however it did not prove any relevant variants.

At the age of 2, the boy was referred to the otolaryngology ambulatory due to OME, which was observed in the otoscopy examination and was present for at least a few months. The impedance audiometry examination revealed a tympanogram type As in the right ear and type B in the left ear. Tympanograms indicated improper compliance: in the right ear 0,23 ml (normal 0,3-1,5 ml), in the left ear it was impossible to detect. There were proper stapedius muscle reflexes in the right ear, meanwhile in the left one they were observed only at the level of 2 kHz and 100 dB HL. That indicated exudative otitis media. The patient received treatment of desloratadine (for 1 month) and mometasone furoate (for 2 months). After 3-month observation of no improvement, he was qualified for bilateral ventilation drainage of the middle ear (Mikołów type).

The procedure was successful, however about 2 months after that, the patient reported to the hospital with unilateral mucous exudation from left ear. The smear was taken and showed the presence of *Achromobacter xylosoxidans* and *Klebsiella oxytoca*, sensitive to the treatment, which included oral amoxicillin for 7 days and ciprofloxacin locally (to the left ear) for 5 days, however it was not successful. After a week, the next treatment applied was cotrimoxazole (sulfamethoxazol + trimetoprim) orally for 14 days and ciprofloxacin locally for 7 days. The symptoms resolved temporarily, only to recur a few days later, when the boy was admitted to the Pediatric Otolaryngology Department with the abundant discharge. We received a positive culture for *Actinomyces oris* and *Streptococcus mitis* with negative tests in the direction of fungal infection. The patient had a 10-days intravenous ceftriaxone treatment with continued local antibiotic. He was discharged from the hospital without any exudate and the clindamycin was prescribed for 7 days to complete the therapy.

Another week after, the symptoms occurred also in the second ear (fig. 1, 2), thus the patient was once more admitted to the hospital in order to undergo detailed diagnostics.

As a diagnostic imaging, the patient had a CT of the temporal bones where no anatomical abnormalities or bone destruction were observed – it did not point to any ear cause. However, coincidentally, it revealed a lack of the posterior nasal spine (fig. 3) – an attachment site for the soft palate, which in this case could cause shortening of the palate.

The boy was receiving amoxicillin with clavulanic acid until the results from the smears came and indicated the MRSA (methicillin-resistant *Staphylococcus aureus*) colonization, thus the treatment changed to intravenous vancomycin for

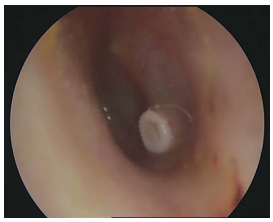

Fig. 1. Otoscopic image after ventilation drainage of the left ear with leakage of thick, mucopurulent secretion

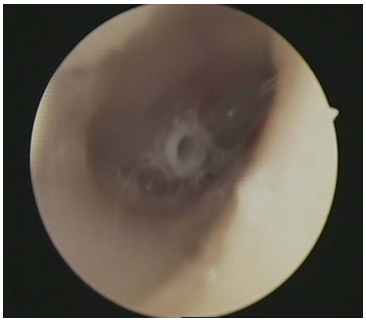

Fig. 2. Otoscopic image after ventilation drainage of the right ear with leakage of thick, mucopurulent secretion

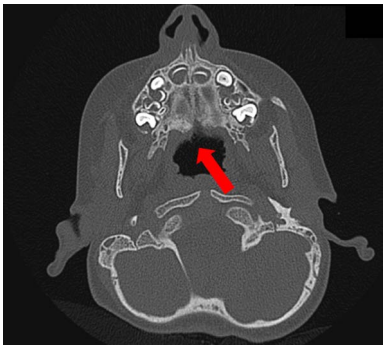

Fig. 3. Computed Tomography (CT) image. Lack of posterior nasal spine – arrow

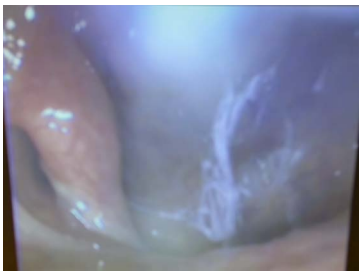

Fig. 4. Flexible nasal endoscopy. Traces of milk in the nasopharynx

7 days. Searching for the reason for the recurring exudates, there was immunological consultation, which excluded other causes such as immunodeficiency.

During the phoniatric consultation, the flexible nasal endoscopy was performed by the phoniatrist (fig. 4), where traces of milk were found in the nasopharynx – it suggested nasal regurgitation of food to the nasopharynx (presumably also to the Eustachian tube) during swallowing. What

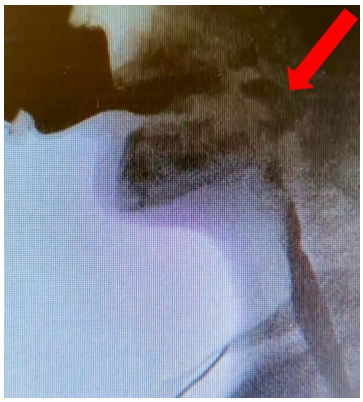

Fig. 5. Videofluoroscopy. Regurgitation of the fluid into the nasopharynx, in the area of auditory tubes – arrow

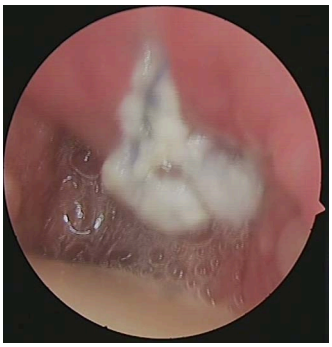

Fig. 6. Videofiberoscopy – posterior pharyngeal flap with fibrin coating and visible sutures

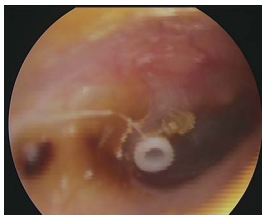

Fig. 7. Otoscopic control image of the right ear. No discharge observed

is more, it revealed a shortened palate without relevant adenoid hypertrophy. As a consequence, the patient was qualified to the videofluoroscopy, where the penetration of fluids to nasopharynx was confirmed (fig. 5).

The lack of closure of the soft palate, confirming VPI in the course of SMCP was found both in the videofiberoscopic and videofluoroscopic examinations.

After making the assumption that the patient may have trumpet reflux causing the constant discharge it was decided to stop antibiotic (vancomycin) treatment after 7 days, but maintain rinsing with boric acid solution and suctioning the discharge. Eventually the patient was qualified for the PPF surgery as a technique of correcting VPI and preventing nasal regurgitation.

As a differential diagnosis, the procedure of nasal mucosa biopsy was also taken during the surgery, to exclude primary ciliary dyskinesia (PCD), which may also be the cause of persistent discharge from the ear and which later proved to be negative.

After the procedure, the wound healing was proper with no bleeding and the pharyngeal flap was properly fixed (fig. 6). Therefore, the patient was dismissed in a good general and local condition. The next control visit was planned in a month – in right ear there was no more exudation immediately after the procedure, in the left ear it stopped after 3 weeks.

On follow-up 4 months after the procedure, there was improvement of patient's condition – he achieved complete velopharyngeal closure and there was no more regurgitation to the openings of auditory tubes as seen in flexible nasal endoscopy. Wound healing proceeded without complications. In addition, proper healing and lack of penetration of liquids and food into the area of openings of the Eustachian tubes during the act of swallowing were observed in follow-up videofluoroscopy test.

During routine checkups he has not presented any discharge until 5 months after operation (fig. 7).

By the issue date of the publication there was one time occurrence of the discharge which occurred during upper respiratory tract infection and has been treated successfully. Shortly after the infection the ventilation tube from the left ear fell out and the effusion formed again as was expected because of his underlying disease. The patient still needs to be under the control of the otorhinolaryngologist, phoniatrist, neurologopedist and pediatric surgeon.

Discussion

Chronic OME is one of the most typical and frequent pediatric disorders. OME can lead to hearing loss that impairs the child's language and behavioral development (16). We can differentiate CSOM and OME with absence of active infection and intact tympanic membrane, which is characteristic for CSOM and presented in our case (17).

The patient was admitted to the ward because of chronic, approximately 3-week, ear discharge. The results from middle ear swabs showed the growth of pathogens for example *Achromobacter xyloxidans* and *Actinomyces oris*. The alarm pathogen MRSA was also detected – all above atypically to cause a middle ear infection. MRSA is a gram-positive bacteria that is very hard to cure, therefore despite multiple antibiotic therapy, including vancomycin, at the beginning no improvement was observed.

For most suspected MRSA patients, treatment includes oral antibiotics such as trimethoprim/sulfamethoxazole, tetracyclines, doxycycline, minocycline and clindamycin. Higher doses of trimethoprim/sulfamethoxazole (160/800 mg, 48 mg/kg in 2 divided doses for children) are recommended for MRSA in patients with normal renal function. Newer drugs such as linezolid, tedizolid and delafloxacin may also be used as alternative oral regimens (18). The patient from the case above received both trimethoprim/

sulfamethoxazole, clindamycin and fluoroquinolones, before fully recovering and getting negative swab results. This shows real difficulty in MRSA elimination from the middle ear environment.

However, though challenging, it is essential to cure the infection in CSOM due to possible spread of the bacteria, leading to intracranial infections and acute mastoiditis. Other problems include hearing loss in varying degrees and, in result, learning difficulties, especially in the speech area (17). To avoid that, the treatment is multidimensional – it can consist not only of systemic antibiotics, but also topical ones, steroids and ear rinsing with topical antiseptics. It is dependent on the particular case, the cause and clinical presentation. If pharmacotherapy is not efficient, the operation (tympanoplasty, middle-ear drainage) is performed (19).

Despite persistent AOM with perforation in tympanic membrane, typically the reasons for CSOM development include mucosal polyps and thickened granular mucosa within the middle ear. Rarely occurring, but one of the most severe cause of CSOM is cholesteatoma. It is important to always take them all into consideration and to exclude them during differential diagnosis (17).

Discharge can also occur in 25-75% children after the procedure of ventilation tube placement. It develops due to infections mostly postoperatively (up to two weeks), but it can recur even for further months because of persistent inflammation and then it is usually treated with antibiotic eardrops with or without corticosteroids, to avoid more severe consequences (20).

In our case, the major problem, which affected the onset of CSOM after ventilation tube placement was VPI with Eustachian tube reflux. It is proven that patients with cranial malformations are prone to chronic non-suppurative otitis media. In literature, CSOM was presented just as a possible, extrapolated outcome (19). We did not find any other similar case. The reasons why SMCP could become the beginning of middle-ear ailments are based in the anatomy and the correlations between incomplete fusion of the soft palate, inefficiency of its muscles, including velopharyngeal sphincter, and Eustachian tube dysfunction. The patient developed, as typical consequences of listed abnormalities, regurgitation and further trumpet reflux and CSOM.

According to SMCP, the patient was qualified for a pharyngoplasty procedure, which is a constantly evolving method. There are two main ways of performing such operations in order to prevent nasal regurgitation: PPF surgery and sphincter pharyngoplasty (21). The patient underwent a PPF procedure including a midline cut and visualization of the muscles. Then, on the posterior wall of the throat, an upper pedunculated flap was incised and sewn in layers into the dissected palate, with particular attention to anastomosis of the muscles. In this way the soft palate could be in contact with posterior pharyngeal wall. The second technique consists of squeezing the upper pharynx, which is important, at the level of the velopharyngeal occlusion (21).

In our patient, nasal regurgitation stopped after surgery. Post-operative fiberoscopy showed complete velopharyngeal occlusion.

Adenoid hypertrophy could mask the symptoms of hypernasality, being a substitute for the valve normally composed of soft palate and lateral pharyngeal walls. Possibly, SMCP could thereby have been asymptomatic to that moment, if CSOM had not appeared (22). In this case, where adenoid was not enlarged, the lack of speech development did not allow to detect hypernasality and therefore postponed diagnosis of SMCP.

The patient also had a biopsy of the nasal mucosa in order to perform differential diagnosis of PCD. Cilia are specialized organelles that project from the surface of most cells and they are essential structures, having wide ranging functions. PCD is a rare and genetically determined syndrome occurring with a frequency of 1:10 000-1:20 000 newborns (23). This disease is inherited in an autosomal recessive manner. The organs affected include, among others: the middle ear, the Eustachian tube or the nasal cavities. Diagnosis can be pursued through a multitest pathway which includes the measurement of nasal nitric oxide, sampling the nasal epithelium to assess ciliary function and structure and genotyping (24). Presented patient did not have PCD proved in biopsy and, by excluding, it proves SMCP as a main source of the problem.

The correct diagnosis of SMCP as a cause of the ear discharge, which was proven by the positive result of PPF surgery gives him a chance for a lasting effect of treatment. However, it requires rehabilitation and follow-up visits, when specialist care, parents' supervision and continuous patient's work are crucial in further speech development.

Conclusions

In CSOM, when the otorrhoea is recurring, specific therapy should be considered, well-matching to the patient's current clinical condition and the antibiogram. Moreover, there are different possible causes, not forgetting more complex ones, which always have to be taken into account. If the pharmacotherapy as a previous treatment is not successful, the underlying cause should be investigated, and when available – the surgical options should be considered.

In patients with SMCP, after surgery it is required to continue with rehabilitation and regular follow-up, especially if there is any complication to this underlying disease, such as CSOM. It is essential to prevent children from further problems with hearing, speech and therefore mental and social development, which could appear if neglected.

Conflict of interest
Konflikt interesów

None
Brak konfliktu interesów

Correspondence
Adres do korespondencji

*Tomasz Lis
Klinika Otolaryngologii Dziecięcej
Warszawski Uniwersytet Medyczny
ul. Żwirki i Wigury 63A, 02-091 Warszawa
tel.: +48 (22) 317-97-21
laryngologia.dsk@uckwum.pl

submitted/nadesłano:
7.07.2023
accepted/zaakceptowano do druku:
28.07.2023

References/Piśmiennictwo

1. Durko T: Zapalenia ucha środkowego. [W:] Śliwińska-Kowalska M (red.): Audiologia kliniczna. Wyd. 1. Mediton, Łódź 2005: 225-230.
2. Principi N, Marchisio P, Esposito S: Otitis media with effusion: benefits and harms of strategies in use for treatment and prevention. Expert Review of Anti-infective Therapy 2016; 14(4): 415-423.
3. Daly KA, Hunter LL, Giebink GS: Chronic otitis media with effusion. Pediatr Rev 1999; 20(3): 85-93; quiz 4.
4. David H, Chi DJK: Zapalenie ucha środkowego. [W:] Licameli GR, Tunkel DE, Szydłowski pe J (red.): Otorynolaryngologia dziecięca – diagnostyka i leczenie. Medipage, Warszawa 2015: 3-11.
5. Massa HM, Cripps AW, Lehmann D: Otitis media: viruses, bacteria, biofilms and vaccines. Medical Journal of Australia 2009; 191(S9): S44-S49.
6. Olszewski J: Ostre zapalenie ucha środkowego. PZWL Wydawnictwo Lekarskie, Warszawa 2022: 16-17.
7. Younis RT, Lazar RH, Long TE: Ventilation tubes and prophylactic antibiotic eardrops. Otolaryngol Head Neck Surg 1992; 106(2): 193-195.
8. Verhoeff M, van der Veen EL, Rovers MM et al.: Chronic suppurative otitis media: a review. Int J Pediatr Otorhinolaryngol 2006; 70(1): 1-12.
9. Alois CI, Ruotolo RA: An overview of cleft lip and palate. Jaapa 2020; 33(12): 17-20.
10. Tuang GJ, Zainal Abidin ZA: Paper-thin roof: submucosal cleft palate with rhinolalia aperta. Postgrad Med J 2022; 98(e1): e63.
11. Reiter R, Brosch S, Wefel H et al.: The submucous cleft palate: diagnosis and therapy. Int J Pediatr Otorhinolaryngol 2011; 75(1): 85-88.
12. Leslie EJ, Carlson JC, Shaffer JR et al.: A multi-ethnic genome-wide association study identifies novel loci for non-syndromic cleft lip with or without cleft palate on 2p24.2, 17q23 and 19q13. Hum Mol Genet 2016; 25(13): 2862-2872.
13. Narożny W, Pilarska E, Kozłowski J et al.: Nagła przemijająca funkcjonalna niewydolność podniebienno-gardłowa u 5-letniego dziecka. Forum Medycyny Rodzinnej 2013; 7(1): 43-46.
14. Ha KM, Cleland H, Greensmith A et al.: Submucous cleft palate: an often-missed diagnosis. J Craniofac Surg 2013; 24(3): 878-885.
15. Nguyen P, Isabella R: Surgical Treatment of Velopharyngeal Insufficiency. [In:] Ho-Hyun S (ed.): Surgical Management of Head and Neck Pathologies. IntechOpen, Rijeka 2021: ch. 6.
16. Vanneste P, Page C: Otitis media with effusion in children: Pathophysiology, diagnosis, and treatment. A review. J Otol 2019; 14(2): 33-39.
17. Morris P: Chronic suppurative otitis media. BMJ Clin Evid 2012; 2012.
18. Siddiqui AH, Koirala J: Methicillin-Resistant Staphylococcus aureus. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2023, StatPearls Publishing LLC. 2023.
19. Chong LY, Head K, Webster KE et al.: Systemic antibiotics for chronic suppurative otitis media. Cochrane Database Syst Rev 2021; 2(2): Cd013052.
20. Venekamp RP, Javed F, van Dongen TM et al.: Interventions for children with ear discharge occurring at least two weeks following grommet (ventilation tube) insertion. Cochrane Database Syst Rev 2016; 11(11): Cd011684.
21. Hortis-Dzierzbicka M, Dudkiewicz Z, Stecko E: Nosowanie otwarte – przyczyny, diagnostyka, sposoby eliminacji. Nowa Pediatria 2000; 18.
22. Hortis-Dzierzbicka M: Rozszczep podśluzówkowy podniebienia. Rozpoznawanie i leczenie. Logopedia 2010-2011; 39-40: 83-92.
23. Horani A, Ferkol TW: Understanding Primary Ciliary Dyskinesia and Other Ciliopathies. J Pediatr 2021; 230: 15-22.e1.
24. Zariwala MA, Knowles MR, Leigh MW: Primary Ciliary Dyskinesia. [In:] Adam MP, Mirzaa GM, Pagon RA et al. (eds.): GeneReviews((R)). Seattle (WA)1993.