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Research

Management of Acute Mastoiditis and Accompanying Complications in Pediatric Patients: Single Center Experience

Pediatrik Hastalarda Akut Mastoidit ve Eşlik Eden Komplikasyonların Yönetimi: Tek Merkez Deneyimi

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ABSTRACT

Objective: Acute mastoiditis (AM) is the most common complication associated with acute otitis media and plays a key role in the development of further complications. We identify the clinical characteristics, management, and outcome of patients with AM and to investigate the relationship between the development of recurrence and the treatment protocol of the first episode.

Methods: Children hospitalized in our clinic due to a diagnosis of AM were retrospectively reviewed. Demographic data, disease-related symptoms, types of complications accompanied by AM, medical/surgical treatment modalities, culture results, laboratory findings, and presence of recurrence were screened. Laboratory findings were compared between those with and without accompanying complications, and between those with and without accompanying intracranial complications.

Results: Of the 58 patients with AM, 24 (41.3%) had isolated AM. Complications associated with AM include subperiosteal abscess (61.7%), sigmoid sinus thrombosis (11.7%), facial paralysis (8.8%), petrositis with subperiosteal abscess (5.8%), meningitis (5.8%), facial paralysis with subperiosteal abscess (2.9%) and, epidural abscess with sigmoid sinus thrombosis (2.9%). Seven patients developed intracranial complications (12%), of whom one had more than one complication. Hemoglobin and hematocrit levels were found to be significantly lower in the presence of accompanying complications (p values, respectively p=0.000, p=0.000). C-reactive protein (CRP) levels were found to be significantly higher in the presence of intracranial complications (p=0.028). Recurrent AM developed in 9 patients (15.5%) during follow-up. There was no statistically significant relationship between the treatment protocol of the first episode and the development of recurrence (p=0.332).

Conclusion: A conservative approach may be preferred for surgical treatment in patients without accompanying intratemporal or intracranial complications. Low hemoglobin and hematocrit levels, with the symptoms and imaging of the patients, may be a warning of the development of accompanying complications, and high CRP values may be a warning of accompanying intracranial complications.

Keywords: Accompanying complications, mastoiditis, otitis media, recurrence

ÖZ

Amaç: Akut mastoidit (AM), akut otitis media ile ilişkili en sık görülen komplikasyondur ve daha ileri komplikasyonların gelişmesinde anahtar rol oynar. AM'li hastaların klinik özelliklerini, yönetimini ve sonuçlarını incelemeyi ve ayrıca nüks gelişimi ile ilk epizodun tedavi protokolü arasındaki ilişkiyi araştırmayı amaçlıyoruz.

Gereç ve Yöntem: AM tanısı ile kliniğimize yatırılan çocuklar geriye dönük olarak incelendi. Demografik veriler, hastalığa bağlı semptomlar, AM'nin eşlik ettiği komplikasyon türleri, tıbbi/cerrahi tedavi modaliteleri, kültür sonuçları, laboratuvar bulguları ve nüks varlığı tarandı. Laboratuvar bulguları eşlik eden komplikasyonu olanlar ve olmayanlar ile intrakraniyal komplikasyonu olan ve olmayan gruplar arasında karşılaştırıldı.

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Bulgular: Elli sekiz hastanın 24'ünde (%41,3) izole AM vardı. AM ile ilişkili komplikasyonlar arasında subperiostal apse (%61,7), sigmoid sinüs trombozu (%11,7), fasiyal paralizi (%8,8), subperiostal apse ile beraber petrosit (%5,8), menenjit (%5,8), subperiostal apse ile beraber yüz felci (%2,9) ve sigmoid sinüs trombozu ile beraber epidural apse (%2,9) yer aldı. Yedi hastada intrakraniyal komplikasyon gelişti (%12) ve bunlardan birinde birden fazla komplikasyon görüldü. Hemoglobin ve hematokrit düzeyleri eşlik eden komplikasyonu olanlarda anlamlı olarak düşük bulundu (p değerleri sırasıyla p=0,000, p=0,000). C-reaktif protein (CRP) düzeyleri intrakraniyal komplikasyon varlığında anlamlı olarak yüksek bulundu (p=0,028). Takipte 9 hastada (%15,5) nüks AM gelişti. İlk epizodun tedavi protokolü ile nüks gelişimi arasında istatistiksel olarak anlamlı bir ilişki saptanmadı (p=0,332).

Sonuç: İntratemporal veya intrakraniyal komplikasyonun eşlik etmediği hastalarda tedavide konservatif cerrahi yaklaşım tercih edilebilir. Düşük hemoglobin ve hematokrit düzeyleri, hastaların semptom ve görüntülemeleri ile birlikte değerlendirildiğinde eşlik eden komplikasyonların varlığı için, yüksek CRP değerleri ise eşlik eden intrakraniyal komplikasyonların varlığı için bir uyarı olabilir.

Anahtar Kelimeler: Eşlik eden komplikasyon, mastoidit, orta kulak iltihabı, nüks

INTRODUCTION

Acute mastoiditis (AM) is the most common complication associated with acute otitis media (AOM), develops when the infection spreads to the mastoid process of the temporal bone and plays a key role in the development of further complications (1,2). In complicated AOM, the purulent infection first causes AM, which leads to further intratemporal and intracranial complications (ICCs), such as sub-periosteal abscess (SPA), facial paralysis (FP), labyrinthitis, petrositis, meningitis, sigmoid sinus thrombosis (SST), and intracranial abscess (2-4). Despite the rational use of antibiotics and advances in imaging and surgical techniques, AM-led complication rates are reported to be between 13% and 38% (5,6). Given the serious nature of intratemporal and but particularly ICCs, their early diagnosis and effective treatment is vital, since delays in their diagnosis and treatment are related to increased morbidity and mortality, and those commonly used antibiotics can suppress the classic signs and symptoms of ICCs (3-7). Temporal bone computed tomography (CT) with intravenous contrast was found to be highly sensitive (97% sensitivity) in evaluating the complications of AOM (4,8). However, the treatment is rather a center-and clinician-dependent; there is still no consensus for managing pediatric AM. Also, management depends on the patient's presentation but may include intravenous antibiotics alone or along with myringotomy and/or ventilation tube (VT) insertion, drainage of the abscess, and cortical mastoidectomy (CM) (2,9,10).

In this study, we aimed to identify the clinical characteristics, management, and outcome of patients with AM, and to investigate differences between laboratory findings between those with and without accompanying complications. Also, we determine the clinical characteristics of patients with recurrent AM, to investigate the relationship between the development of recurrence and the treatment protocol used in the first episode.

METHODS

A retrospective study was conducted at our tertiary referral hospital between January 2014 and June 2020 over six years. The study protocol was approved by the Bakırköy Dr. Sadi Konuk Training and Research Hospital's local ethics board (decision no: 2020-18-07, date: 07.09.2020). The medical charts of children hospitalized in our Otorhinolaryngology clinic due to AM were retrospectively reviewed. The diagnosis of AM is based on clinical signs of AOM (ongoing or within 14 days) associated with retro-auricular signs of infection: swelling, erythema, tenderness, protrusion of the auricle, and decrease in the posterior upper wall of the external ear canal. Also, the diagnosis of AM was confirmed by imaging methods, CT scan of the temporal bone with fine cuts in all patients, and magnetic resonance imaging testing for patients with suspected ICCs. The demographic data of the patients, disease-related symptoms, complications accompanied by AM, the month of application, laboratory data [white blood cell count (WBC), C-reactive protein (CRP), red blood cell count, hematocrit (Hct), neutrophil count, lymphocyte count, neutrophil-to-lymphocyte ratio, microbiological cultures], length of hospital stay, medical and/or surgical treatments, and outcome were recorded.

Children with immunodeficiencies or craniofacial malformations and children presenting with AM found to be because of underlying chronic otitis media with/without cholesteatoma were excluded from the study.

On admission, we used sterile swab sticks to collect a specimen of the ear discharge. In cases of surgical intervention, we collected the pus during surgery. All patients received empiric intravenous antibiotics shortly after the admission and supportive therapy if needed. When there was no response to iv antibiotics for 24/48 hours surgical intervention was performed in patients with no accompanying complications and performed in all patients in the presence of accompanying complications (Figure 1). Medical treatment was performed in all patients collaboration with the pediatrics department. If there was suspicion of ICCs, a multidisciplinary approach was used for

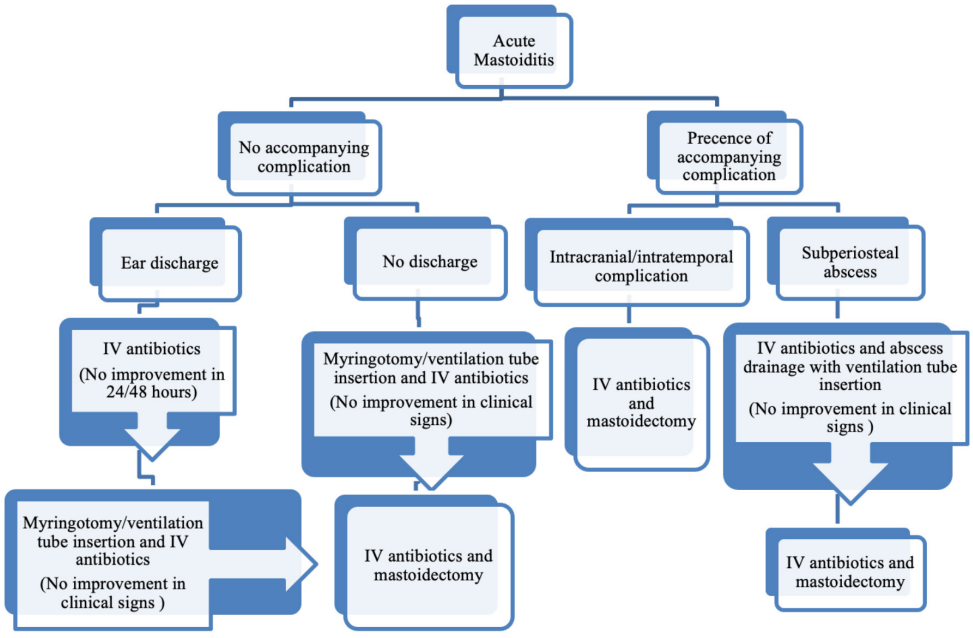

Figure 1. Management algorithm of acute mastoiditis in children

diagnosis and management, and the patient was transferred to the pediatrics department if needed.

Recurrent AM was defined as an episode of AM over 4 weeks after a previous episode and in the absence of symptoms or findings to suggest persistent infection between episodes (11). Records were surveyed for readmission or treatment for recurrent AM in the affected ear.

Statistical Analysis

NCSS (Number Cruncher Statistical System, Kaysvilee, UT) 2007 software was used for the statistical analysis. Descriptive statistical analyzes were performed. Mean values were compared with Mann-Whitney U test. The relationship between recurrence and age, surgery type, accompanying complications, and ICCs were analyzed with Fisher's Exact test. In all analyses, $p<0.05$ was considered to indicate statistical significance.

RESULTS

Over 6 years, 58 patients were hospitalized in our clinic due to AM. Of these 58 patients, 25 were female (43.1%) and 33 were male (56.9%). The mean age was 4.91±3.97 (0-16) years. There were 7 patients under one year of age (the youngest was 2 months old and the oldest was 9 months old). When calculating the mean age, the ages of these patients were accepted as 0 years. The demographic data and the age distribution of the patients are shown in Table 1. The average length of stay in the hospital was 11.5±8.86 (3-41) days. Most of the patient admissions were in the winter months.

When the complaints at the admission of the patients were evaluated, the most common symptoms were found to be otalgia, retro-auricular swelling-hyperemia, protruding of the auricle, and otorrhea. 34 (58.6%) out of 58 patients, had complications [SPA, SST, FP, petrositis, meningitis, and epidural abcess (EA)] accompanied by AM. There was more than one accompanying complication in 4 patients (SPA and petrositis in two patients, SPA and FP in one patient, SST and EA in one patient). SPA was the most common complication (n=24, 41.3%). 7 patients (12%) had ICCs, of whom one had multiple concurrent ICCs. The most common ICC was SST (n=5, 8.6%), followed by meningitis (n=2, 3.4%). Of the four patients with FP, one was Hause-Brackmann grade 4, two were grade 3, and one was grade 2.

Table 1. The demographic data and the age distribution of the patients

		n (%)
Gender	Male	33 (56.9%)
	Female	25 (43.1%)
Side	Right	32 (55.2%)
	Left	26 (44.8%)
Age (years)	<1	7 (12%)
	1-4	24 (41.4%)
	4-8	18 (31%)
	>8	9 (15.6%)

At admission, an empiric intravenous antibiotic treatment was administered to all patients after taking samples for culture if there was ear discharge. Samples for culture were taken during the surgical intervention from those who had no ear discharge at admission. According to the clinical condition of the patient, as a first-line antibiotic treatment, we used ceftriaxone (50-100 mg/kg) as monotherapy in 22 patients (37.9%), along with clindamycin (15-40 mg/kg) or metronidazole (20-40 mg/kg) in 24 patients (41.3%). Vancomycin (60 mg/kg) or meropenem (120 mg/kg) was preferred in certain patients depending on clinical symptoms or culture results in the line with pediatric infectious disease department recommendations. Intravenous corticosteroids (1 mg/kg prednisolone) were administered to patients with accompanying FP. All patients who initially presented with FP had fully recovered. For managing the five SST patients, one was placed on anticoagulation therapy for 45 days. During the follow-up, minor bruising was noted for this patient and no other bleeding concerns were reported. Of the four patients who were not anticoagulated, two had a nonocclusive thrombus and two had no progression of their thrombus on imaging studies during their hospital stay. No patient died during the hospital stay or follow-up.

When considering surgical management, a conservative

Table 2. Symptoms at admission, type, and management of accompanying complications and microbiological profile of patients with acute mastoiditis

		n (%)
Symptoms at admission	Otalgia	36 (62%)
	Retroauricular swelling-hyperemia	25 (43.1%)
	Protruding of the auricle	21 (36.2%)
	Otorrhea	21 (36.2%)
	Headache	19 (32.7%)
	Fever	17 (29.3%)
	Irritability	9 (15.5%)
	Vomiting	4 (6.8%)
	Facial paralysis	4 (6.8%)
	Neck stiffness	1 (1.7%)
Accompanying complications (n=34)	Subperiosteal abscess	21 (61.7%)
	Subperiosteal abscess + petrositis	2 (5.8%)
	Subperiosteal abscess + facial paralysis	1 (2.9%)
	Facial paralysis	3 (8.8%)
	Sigmoid sinüs thrombosis	4 (11.7%)
	Sigmoid sinüs thrombosis + epidural abscess	1 (2.9%)
	Meningitis	2 (5.8%)
Treatment protocol	Medical	16 (27.5%)
	Medical + VT	8 (13.7%)
	Medical + drainage + VT	16 (27.5%)
	Medical + CM + VT	18 (31%)
Microbiology	Negative	11 (26.8%)
	Streptococcus pneumoniae	17 (41.4%)
	Pseudomonas aeruginosa	5 (12.1%)
	Streptococcus pyogenes	5 (12.1%)
	Enterococcus species	2 (4.8%)
	Escherichia coli	1 (2.4%)

VT: Ventilation tube, CM: Cortical mastoidectomy

Table 3. The clinical characteristics of patients with recurrent AM

	Age at the first episode	Gender	Accompanying complications in the first episode	Culture results of the first episode	Treatment modalities of the first episode
Patient 1	5 month	F	SPA	*Streptococcus pneumoniae*	Medical + drainage + VT
Patient 2	6 years	M	SST	No growth	Medical + CM + VT
Patient 3	4 years	M	None	*Streptococcus pneumoniae*	Medical
Patient 4	7 years	M	SPA + petrositis	*Streptococcus pneumoniae*	Medical + CM + VT
Patient 5	3 years	F	SPA	No growth	Medical + drainage + VT
Patient 6	5 years	F	FP	No growth	Medical + CM + VT
Patient 7	9 years	F	None	No growth	Medical + VT
Patient 8	4 years	F	None	No growth	Medical + VT
Patient 9	6 years	M	None	No growth	Medical

SPA: Subperiosteal abcess, SST: Sigmoid sinus thrombosis, FP: Facial paralysis, VT: Ventilation tube, CM: Cortical mastoidectomy, AM: Acute mastoiditis

Table 4. The comparison of blood parameters in patients with and without accompanying complications and with and without ICCs

	Accompanying complication (n=34) (mean ± SD)	No accompanying complication (n=24) (mean ± SD)	p-value	ICCs (n=7) (mean ± SD)	No ICCs (n=51) (mean ± SD)	p-value
Hb (g/dL)	10.72±1.31	13.04±1.40	**0.000**	10.60±0.57	11.8±1.82	0.081
Hct (%)	33.09±4.03	39.31±3.74	**0.000**	33.05±2.23	36.02±5.14	0.090
WBC (10^3/IU)	15.44±6.16	10.79±4.29	**0.004**	12.02±4.02	13.72±6.11	0.527
NLR	2.65±2.11	3.34±3.21	0.528	4.47±3.14	2.72±2.50	0.185
CRP (mg/L)	37.7±37.0	24.1±28.6	0.114	66.4±60.6	25.4±25.8	**0.028**

n: Number, SD: Standard deviation, ICC: Intracranial complication, Hb: Hemoglobin, Hct: Hematocrit, WBC: White blood cell count, NLR: Neutrophil to lymphocyte ratio, CRP: C-reactive protein (Bold text indicates a statistically significant difference with a p-value less than 0.05)

approach was adopted in patients without ICCs. Sixteen patients (27.5%) were treated without surgical intervention. Eight patients (13.7%) underwent myringotomy + VT insertion. Twenty one (87.5%) of 24 patients with a SPA underwent incision and drainage of the abscess + VT insertion, and later 5 (23.8%) of these 21 patients underwent CM + VT insertion, during the same admission, due of lack of clinical improvement. This was performed on average 4 days after the original surgery. The remaining three patients with SPA underwent CM + VT insertion. Of these three patients, two had concomitant petrositis and one had FP. Ten of the 18 patients who underwent CM + VT insertion, three had FP, two had meningitis, four had SST, one had SST + EA.

Culture results were not available for 17 (29.3%) patients. Of the remaining 41 patients (70.6%) no growth was observed in 11 (26.8%), *Streptococcus pneumoniae* was isolated in 17 (41.4%), and the other bacteria in 13 (31.7%) patients. The symptoms at admission, type and management of accompanying complications, and microbiological profile of the patients are shown in Table 2.

Recurrent AM developed in 9 patients (15.5%) during follow-up. The time from the first AM to the second episode ranged from 6 weeks to two years. The clinical characteristics of patients with recurrent AM are shown in Table 3. There was no statistically significant difference in terms of recurrence between those with and without accompanying complications and those with and without ICCs (Fisher's Exact test, p=0.555, p=0.70). Also, there was no statistically significant relationship between the treatment protocol of the first episode and the development of recurrence (Fisher's Exact test, p=0.332).

Patients with and without complications accompanying AM were compared in terms of blood parameters, hemoglobin and Hct levels were found to be significantly lower (p values, respectively p=0.000, p=0.000), WBC levels were found to be significantly higher in the presence of accompanying complications (p=0.004). When patients with and without

ICCs were compared in terms of blood parameters, the CRP levels were found to be significantly higher in the presence of ICCs (p=0.028). The comparison of blood parameters in patients with and without accompanying complications and with and without ICCs is shown in Table 4.

DISCUSSION

In this study, we reported the clinical characteristics, management, and outcome of our patients with AM and compared blood parameters with and without accompanying complications and those with and without ICCs in children attending a large tertiary referral care center, covering a population of two million people.

Similar to the work of Ren et al. (11), we found, as expected, the highest rates of AM-related hospitalizations were highest in winter and lowest in summer, reflecting the seasonal variation of viral upper airway infections closely related to the development of AOM. In the line with previous studies, the most common presenting symptoms were otalgia, retro-auricular swelling-hyperemia, and protruding of the auricle (2,4). Only 17 patients (29.3%) had fever at admission. Although it is thought that this may have been due to the antibiotic treatment they may receive before, previous treatment data were not available for children in our study.

In our study, isolated AM was seen in 24 (41.3%) patients. The most common accompanying complication was SPA (n=24, 41.3%), followed by SST (n=5, 8.6%) and FP (n=4, 6.8%). ICCs were seen in 7 (12%) patients. Duygu and Şevik Eliçora (2) reported the rate of SPA as 28.6%, SST as 7.1%, and FP as 25% in complicated pediatric AM cases. Inconsistent with our study, Mattos et al. (4) reported the rate of SPA as 38%, SST as 8.3%, and FP as 16.7% in complicated pediatric AM cases. Mansour et al. (3) stated that although AM rates decreased with the introduction of antibiotics, the rate of ICCs due to AM remained high, ranging from 5% to 29%, and they reported the ICC development rate as 13% in their study. Similarly, we found the rate of ICC development due to AM to be 12%.

Although studies have described various treatment algorithms in the literature, no consensus has been reached yet in the treatment of AM and accompanying complications (2,5,12-14). Mierzwiński et al. (12) stated that incision and drainage of SPAs have disadvantages like poor cooperation and difficult daily wound toilet in children, it may require multiple episodes of general anesthesia and the inability to expose other existing complications of AM, such as EA which can be detected and immediately treated during mastoidectomy. They reported that they recommended mastoidectomy also in SPAs, performed mastoidectomy in 77% of the patients and a recurrence rate of 8% in their series of 73 cases. Psarommatis et al. (13) reported that nine out of 21 (42.9%) patients who had the first incision and drainage of a SPA needed mastoidectomy as they did not improve over time. Ghadersohi et al. (14) stated that favorable outcomes for children treated with otherwise uncomplicated AM with SPA who are managed with incision and drainage, myringotomy ± tympanostomy tube placement, and intravenous antibiotics. They reported that they reserved mastoidectomy to treat patients with ICCs and certain intratemporal complications, such as acute petrositis and labyrinthitis. However, recurrent AM rates were not available in their series of 48 cases. Duygu and Şevik Eliçora (2) stated that they performed a mastoidectomy if progression occurs despite a perforated tympanic membrane, or severe clinical presentation with multiple complications together with ICCs. In our practice, we performed a stepwise approach to AM and its accompanying complications. In isolated AM cases, if the tympanic membrane is perforated and pus drainage is sufficient, we only administered intravenous antibiotic therapy, if the tympanic membrane is not perforated or pus drainage is not sufficient from perforation, we performed myringotomy and VT insertion together with intravenous antibiotics. None of the patients with isolated AM required additional intervention. All the patients in our study with a SPA, without other complications, underwent myringotomy + VT insertion and incision and drainage of the abscess together with intravenous antibiotics. Due to the lack of clinical improvement, five (23.8%) of these patients required CM during the same admission. There were three patients with SPA who underwent CM + VT insertion in the first-line, because of the co-occurrence of a petrositis in two patients and FP in one patient. Also the patients with accompanying FP (n=3, 8.8%), meningitis (n=2, 5.8%), SST (n=4, 11.7%) and SST + EA (n=1, 2.9%) were managed with CM + VT insertion together with intravenous antibiotics in the first-line treatment. To the best of our knowledge, there are only a few studies in the literature that have focused on recurrent AM cases. Recurrent AM developed in 9 patients (15.5%) during the follow-up in our series of 58 cases. We performed the same stepwise management approach in the recurrent cases and we did not find a statistically significant relationship between the treatment protocol of the first episode and the development of recurrence. Based on these data and in the absence of formal national guidelines, we believe that our treatment protocol is sufficient for children with presenting AM.

Information on bacterial cultures was available for 41

(70.6%) patients and more than a quarter of these patients revealed 'no growth' samples. This may relate to previous treatments that they may have received and could reduce the probability of recovering causative bacteria. However, previous treatment data were not available in our study and the lack of this information represents one of our study's limitations. In the current opinion, *Streptococcus pneumoniae* is considered the predominant pathogen in children affected by AM (15). *Streptococcus pneumoniae* were the predominant pathogen in our study and this finding supports the current opinion.

Golz et al. (16) reported in their study that children with anemia had more otitis media attacks compared with healthy children with normal hemoglobin levels, and they also found a direct relationship between anemia and the number of AOM episodes. Although it varies according to gender and race in children, a hemoglobin level below 10.5 g/dL between 6 months and 2 years of age and below 11.5 g/dL between 2 years and 12 years of age is considered anemia (17). Based on this information, when we analyzed our data, we found statistically significant differences in laboratory findings between those with and without complications accompanying AM at the time of admission. As shown in Table 4, we found that mean Hb and Hct levels in the presence of accompanying complications were 10.72±1.31 g/dL and 33.09±4.03% and we found these values were significantly lower and WBC levels were significantly higher in the presence of accompanying complications. Mansour et al. (3) with the object of identifying those AM patients who are at a high risk of developing ICC, thus supporting their immediate brain imaging upon AM diagnosis, compared the clinical information available at the time of AM diagnosis in patients who developed and those who did not develop imaging-diagnosed ICCs and they reported that high CRP levels increased the risk of imaging-diagnosed ICCs. Similarly, Duygu and Şevik Eliçora (2) compared CRP values between the AM patients with and without ICCs and they reported that they found CRP values significantly higher in patients with accompanying ICCs. We also found CRP levels were significantly higher in the presence of ICCs.

The major limitation of our study is its retrospective nature. Due to its retrospective nature, we didn't have previous treatment and vaccination information data. Although pneumococcal vaccination was introduced in our country in 2009, the predominant pathogen was found to be *Streptococcus pneumoniae* in our study. To explain this predominance and influence of vaccination on accompanying complications, we think that large case series including previous vaccination data are needed.

CONCLUSION

AM is the most common complication associated with AOM in children. The most common symptoms in the children with AM were otalgia, retro-auricular swelling-hyperemia, protruding of the auricle, and otorrhea. Since no statistically significant relationship was found between the treatment protocol of the first episode and the development of recurrence, a conservative approach may be preferred for surgical treatment in patients without accompanying intratemporal or ICCs. Low hemoglobin and Hct levels with the symptoms and imaging of the patients may be a warning for developing accompanying complications, and high CRP values may be a warning for accompanying ICCs.

ETHICS

Ethics Committee Approval: The study protocol was approved by the Bakırköy Dr. Sadi Konuk Training and Research Hospital's local ethics board (decision no: 2020-18-07, date: 07.09.2020).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: M.A.A., H.A.U., M.Y., F.G., N.H., Concept: M.A.A., H.A.U., M.Y., P.S., F.G., N.H., Design: M.A.A., H.A.U., M.Y., P.S., F.G., N.H., Data Collection or Processing: M.A.A., H.A.U., M.Y., P.S., F.G., N.H., Analysis or Interpretation: M.A.A., H.A.U., M.Y., P.S., F.G., N.H., Literature Search: M.A.A., P.S., F.G., N.H., Writing: M.A.A., H.A.U., M.Y., P.S., F.G., N.H.

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