

Does Chronic Immune Thrombocytopenia Lead to Hearing Loss?

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ABSTRACT

Objective: We aimed to investigate the incidence of hearing loss in patients followed up for Chronic Immune Thrombocytopenia Purpura (ITP).

Material and Methods: All patients over the age of 18 who referred to the hematology outpatient clinic between January and June 2020 and followed up with the diagnosis of Chronic ITP were included in the study. Hearing tests of patients diagnosed with Chronic ITP and received first-line treatment (IVIg and corticosteroid) for any reason other than ear diseases during their treatment were evaluated retrospectively. Patients with a history of hearing loss, perforation of the tympanic membrane or who had any squeal due to a previous chronic ear infection and patients who had a previous ear operation were excluded from the study. In addition, patients' age, gender, time of ITP diagnosis, platelet values at the time of diagnosis, platelet values during audiological evaluation, concomitant disease, history of splenectomy, additional drug use and ISTH-SSC Bleeding Evaluation Score data were also recorded.

Results: Of the 34 cases, 58.8% (n=20) were female and 41.2% (n=14) were male. The mean age was 49.06±18.26. Similarly, when compared, usage of IVIg/Methylprednisolone, IVIg/ Methylprednisolone /Eltrombopag, and IVIg/Methylprednisolone /Rituximab/Eltrombopag was not found to be a factor that would cause hearing loss (p>0.05). No statistical correlation was found between ISTH-SSC and time of diagnosis (months) and hearing loss (p>0.05).

Conclusion: Parameters such as various drugs used in the course of Chronic ITP disease, age, gender, time of diagnosis, and presence of concomitant disease do not cause hearing loss.

Keywords: Chronic ITP, hearing loss, inner ear hemorrhage, thrombosis

INTRODUCTION

Immune Thrombocytopenia Purpura (ITP) is an autoimmune disease characterized by increased peripheral immune-mediated platelet destruction and impaired platelet production in megakaryocytes. The newly diagnosed ITP is defined as ITP within first 3 months from diagnosis, Persistent ITP within 3-12 months from diagnosis without spontaneous remission, or for cases that cannot remain in remission when treatment is stopped (1). Chronic ITP is an autoimmune bleeding disorder that lasts more than 12 months with thrombocyte values <100,000 / mm³ and there is no additional disease to explain this condition (2). Although in some patients single episodes of ITP early remission are experienced, up to 70% of adults develop Chronic ITP (3). ITP occurs with an incidence rate of 1.6 to 3.9 per 100,000 patient-years, which increases with age and has a slight female preponderance worldwide (4). Similarly, it has an annual incidence of 2.92 / 100,000 and a prevalence of 35.1 / 100,000 in Turkey (5,6).

There is a wide spectrum of presentations from mild cases with petechiae and ecchymosis on the skin to severe mucocutaneous bleeding, even life-threatening bleeding (7). Although the risk of critical-serious bleeding such as intracerebral hemorrhage is quite low (about 1%) in ITP patients, a history of previous bleeding, platelet values <10,000 / microL, and being <60 years of age increase the risk of bleeding (8). The risk of venous thromboembolism in ITP patients is twice as high when compared to the general population (9).

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Hearing loss is a condition that can be caused by a wide variety of etiologies. Developmental losses, advanced age, infectious conditions, middle ear pathologies, trauma, otosclerosis, exposure to loud noise, Meniere's, chronic diseases, autoimmune and central causes and some drugs (aminoglycosides, erythromycin, tetracycline etc.) are included in etiology [10]. In addition, bleeding or vascular occlusion can cause hearing loss [11]. For maintaining the ion and fluid balance of the inner ear, sufficient blood supply to the cochlea is necessary and essential for normal hearing function. If cochlear microcirculation (e.g., intralabyrinthine hemorrhage) is interrupted. It may result in dysfunction of hearing and balance [12]. Intralabyrinthine hemorrhage (ILH) is a rare complication in patients with hematological disease and / or under anti-coagulant therapy [11].

In our study, we aimed to investigate the incidence of hearing loss in Chronic ITP patients undergoing different treatment protocols and whether the loss is due to bleeding in the vascular structures of the inner ear or secondary to the development of treatment-related thrombosis.

To our knowledge, this is the first study about Chronic ITP's affect on hearing levels.

MATERIAL and METHODS

The available data of all patients over 18 years of age who were followed with a diagnosis of Chronic ITP in the hematology outpatient clinic were retrospectively analyzed. The ethical approval was taken from the local ethical committee (prot.no:2021/514/197/1). Thirty-four patients some received first step (IVIG and corticosteroid) treatment and some second step treatment (splenectomy, rituximab, immunomodulatory drugs) were included in the study. All of the patients were examined in the otolaryngology clinic by the same specialist. Patients with known chronic ear disease and known hearing loss, who had an abnormal appearance in the tympanic membrane, those who did not want to participate in the study voluntarily, and the ones with the diagnosis of secondary ITP were excluded from the study. Patients who had history of drug use with known ototoxic effects such as aminoglycosides, tetracycline, vancomycin or chemotherapeutic drugs as cisplatin, carboplatin, bleomycin or chloroquine, quinine and furosemide were excluded from the study.

None of the patients were under corticosteroid therapy at the time of pure tone audiometry tests. However, corticosteroid (methylprednisolone) was present in the past treatment history of all patients for which it is the most commonly used group of drugs in the first-line treatment of ITP.

Pure tone audiometry was performed to all patients regardless of the time of diagnosis and treatment. In addition, patients' age, gender, duration of diagnosis, diagnosis platelet values, accompanying disease (diabetes, coronary artery disease, hypertension, kidney and liver disorders, etc.), splenectomy, additional drug use, and ISTH-SSC Bleeding Assessment Score data were also recorded.

Statistical Analysis: The compatibility of the data to normal distribution was examined with the ShapiroWilk test. Comparison of normally distributed characteristics in two independent groups was performed using Student's t test One-way analysis of variance, and comparison of more than two independent groups were done using (ANOVA) and LSD multiple comparison tests. Mann Whitney u test was used for the comparison of non-normally distributed features in two independent groups, and Kruskal Wallis test and All pair wise multiple comparison tests were used in comparison of more than two independent groups. Relationships between numerical variables were tested with Spearman rank correlation coefficient. The relationship between two categorical variables was examined using the Exact Chisquare test. In addition, the relationship between hearing loss and independent variables was examined using the multivariate binary Logistic Regression (enter) model.

As descriptive statistics, mean \pm standard deviation, median, min and max for numeric variables, number and % values for categorical variables were presented.

SPSS Windows version 23.0 package program was used for statistical analysis and $p < 0.05$ was considered statistically significant.

RESULTS

Of all patients, 20 (58.8%) were women, and 14 (41.2%) were men, with a mean age of 49.06 ± 18.26 . In pure tone audiometry averages of air and bone conductions were; right air conduction (17.68 ± 13.84), left air conduction (17.61 ± 13.66), right bone conduction (10.84 ± 14.14), left bone conduction (11.19 ± 13.92). Mild to moderate sensorineural hearing loss was detected in 5 of the patients included in the study. Thrombocyte values at the time of audiometric test were observed as (174781.25 ± 91186.70). (Table 1)

There was statistically no significant difference in air and bone conduction results in both ears in women and men, patients with different drug history and patients with and without splenectomy ($p = 0.377$).

There was no significant difference between the mean age of those with hearing loss 51.80 ± 17.88 (56) and the mean age of those without hearing loss 48.11 ± 18.75 (53.50) ($p = 0.686$). Similarly, ISTH-SSC scores and time to diagnosis not significantly different in both groups ($p > 0.05$).

A statistically significant relationship was found between drug use and hearing loss ($p = 0.028$). It was observed that the use of IVIG/ methylprednisolone and IVIG/ methylprednisolone/Eltrombopag was high in patients with no hearing loss, while the use of IVIG/ methylprednisolone/Rituximab/Eltrombopag and others(methylprednisolone/IVIG+ immunosuppressant agents) was significantly more used in the group in patients with hearing loss (Table 2).

Table 1. Demographic properties of patients and drugs used

Age mean±sd (M) (min-max)	49,06±18,26 (55) (23-85)	
Right air conduction mean±sd (M) (min-max)	17,68±13,84 (12) (5-58)	
Right bone conduction mean±sd (M) (min-max)	10,84±14,14 (5) (0-53)	
Left air conduction mean±sd (M) (min-max)	17,61±13,66 (15) (5-55)	
Left bone conduction mean±sd (M) (min-max)	11,19±13,92 (7) (0-50)	
Gender n(%)		
Male	14 (41,2)	41,2
Female	20 (58,8)	58,8
Drugs used n(%)		
IVIG/Methylprednisolone	17 (50)	50,0
IVIG/Methylprednisolone/Eltrombopag	4 (11,8)	11,8
IVIG/Methylprednisolone / Rituximab /Eltrombopag	4 (11,8)	11,8
Other (Prednol/IVIG+immunosuppressant agents)	9 (26,5)	26,5
Splenectomy n(%)		
Yes	7 (20,6)	20,6
No	27 (79,4)	79,4

Table 2. Relationship analysis of hearing loss between age, medication used, duration of diagnosis and ISTH-SSC score

	Hearing Loss		p
	Positive (n=5) Mean±sd (M)	Negative (n=28) Mean±sd (M)	
Age	51,80±17,88 (56)	48,11±18,75 (53,50)	0,686
ISTH-SSC	0±0 (0)	0,50±0,75 (0)	0,173
Drugs Used n(%)			
IVIG/Methylprednisolone	0 (0)	17 (60,7)	0,028
IVIG/Methylprednisolone/Eltrombopag	0 (0)	3 (10,7)	
IVIG/Methylprednisolone/Rituximab/Eltrombopag	3 (60)	5 (17,9)	
Others(Methylprednisolone/IVIG+immunosuppressant agents)	2 (40)	3 (10,7)	
Duration of diagnosis (months)	46,41±26,01 (34,5)	93,28±85,20 (61,35)	0,509

DISCUSSION

Hearing loss is a condition that negatively affects people's quality of life and can be caused by a wide variety of drugs. Although hearing loss can occur due to many different etiologies, it can also be seen due to drug use or inner ear blood supply disorder.

In the case of ototoxicity, sensorineural hearing loss occurs as a result of damage to the cochlear cells in the inner ear, while balance disorders are observed if damage occurs in the vestibular system [13].

Chau et al. reported that sudden hearing loss may result due to vascular causes, and these may be due to cardiovascular diseases, subdural hematoma, pontine hemorrhage, transient ischemic attacks, sickle cell anemia or hemodialysis coagulopathy [14]. Some authors believe that blood viscosity and plasma changes create perfusion disturbances [15].

As a result of the widespread use of Magnetic Resonance Imaging (MRI) acute sensorineural hearing loss (SNHL) due to hemorrhage in inner ear has been reported in the literature [16]. Also, especially in patients with underlying coagulation disorders, cases of SNHL as a result of ILH have been reported [17,18]. None of our patients developed a clinical thrombosis that could cause hearing loss, which suggests that the inner ear structures are not impaired due to thrombotic plugs in our patients. The thrombocyte count of the patients in our study was not at critical low values such as 10,000/micro L and with close follow-ups of thrombocyte counts that no serious bleeding side effects were observed. We thought this was the absence of hearing loss due to ILH.

In a long-term study about the incidence of thrombosis in ITP patients, in some patients thrombotic events (both arterial and venous) occurred, and the median platelet count at thrombotic events was found as $102 \times 10^9/L$. It was not that smoking, hypertension, male gender, history of thrombosis, and atrial fibrillation (AF) were significantly associated with thrombosis [19]. We think the reason why we did not detect hearing loss even with high platelet values in some patients, because our patients were mostly female, none of them smoke, only 1 had atrial fibrillation history, and none had a previous thrombosis history.

Mild to moderate sensorineural hearing loss was detected in 5 of the patients included in our study. All of these were losses that were found incidentally in our study, none of them was acute SNHL; it may be the result of oral steroids which all of the patients have at least once used. When the patients with hearing loss were evaluated, it was found that all of them had at least one additional disease. Hearing loss was seen significantly high in patients who got IVIG/methylprednisolone /Rituximab/Eltrombopag and others (methylprednisolone/IVIG+ immunosuppressant) treatment. But in the literature there is no evidence of SNHL due to drugs used during ITP treatment such as Rituximab, Eltrombopag, Vincristine [20,21]. Since we had a very small group of patients we believe that to say these drugs cause hearing loss, a more detailed analysis of hearing levels during the use of these specific drugs will give more accurate answers. In these patients, no specific difference was found in terms of age, gender, platelet values, mean diagnosis, and treatment times, or that could cause hearing loss.

One thing to explain this can be that since these hearing losses were mild to moderate patients were not aware of it or it may be that they were aware but since it did not affect their daily life, they did not seek any medical help.

According to the ISTH-SSC bleeding risk score (ISTH-SSC Bleeding Assessment Tool) one patient scored 3 and one patient 2 at the time of diagnosis and during follow-up [22]. No hearing loss was observed in these patients. When 5 patients with hearing loss were evaluated, it was found that they all had ISTH-SSC bleeding risk scores were 0. Due to the patients' low bleeding score, we did not evaluate this hearing loss as a bleeding complication. Since there was no evidence of bleeding or thrombosis in the inner ear it was thought that no hearing loss emerged. In addition, we think that the median age of our patients is 49.06 ± 18.26 , and the thrombocyte count is not low at critical values such as 10,000 / microL, which reduces the risk of serious bleeding in the course of the disease and, thus, the risk of hearing loss due to bleeding. We have some limitations in our study. We worked with a small number of patients. Patients' hearing levels were evaluated once, and patients were at different time intervals of their treatment.

CONCLUSION

We can say that parameters such as age, gender, time of diagnosis or concomitant diseases do not cause hearing loss. If bleeding or thrombosis does not occur during treatment, it is less likely to see hearing loss.

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