Abstract. Melanotic neuroectodermal tumor of infancy (MNTI) is a rare infantile tumor that originates from mesenchymal-neuroectodermal cells, the treatment of which uses platinum derivatives that can affect hearing loss. The present study evaluated the long-term effects of ototoxicity following chemotherapy with cisplatin, vincristine, cyclophosphamide, teniposide and adriamycin in a 10-year-old patient after surgical removal of a MNTI tumor at the age of 8 months. Audiometric tests (high-frequency tonal audiometry, speech audiometry, speech acoustics, tympanometry and absorbance measurements) were performed during a 10-year follow-up after receiving chemotherapy. Hearing disorders in the high-frequency range (6,000 to 16,000 Hz range) were demonstrated for both ears, indicating that these may be the long-term effects of chemotherapy with use of platinum compounds during the treatment of infants.

Introduction

Melanotic neuroectodermal tumor of infancy (MNTI) is a mixed mesenchymal-neuroectodermal tumor characterized by the presence of pigment cells containing melanin, which usually appears in the first year of life (1). The tumor is benign, but due to its rapid growth, it can damage the surrounding structures, which makes it dangerous (2). Most commonly, the tumor is located in the anterior part of the alveolar process; less frequently in the skull, brain or mandible (3). The treatment of choice is surgical excision of the tumor and chemotherapy (4). Chemotherapy is one of the primary methods of treatment in cancer therapy, but it may be associated with specific side effects (5). The most commonly used anti-cancer drug is cisplatin, which has a nephrotoxic and ototoxic impact (6). Chemotherapy based on platinum compounds is very useful in the treatment of neuroectodermal neoplasms in children. Unfortunately, their use can lead to morbid infections (7,8) as well as irreversible hearing loss (9). Literature data show that between 40 and 80% of cisplatin-treated patients experience permanent hearing loss (10,11). Some authors report that cisplatin-induced ototoxicity has been observed in 7 and 90% of cases at standard doses (12), as well as at different doses and in various age groups (13), including children (14). Clinically, ototoxicity manifests itself as bilateral hearing loss accompanied by tinnitus (15). Hearing loss begins in the high-frequency range and progresses towards lower frequencies (16,17).

As a consequence, ototoxicity can lead to delayed speech development, learning difficulties, and even a deterioration in psychosocial, emotional and general psychological well-being (16). Also, ototoxicity has been shown to have a progressive nature (11,15). Hearing impairment or delayed hearing loss can appear a few years after the end of treatment. Therefore, long-term specialist monitoring of the condition of the auditory system for a minimum of 10 years is recommended. Ototoxicity risk factors include the cumulative dose, impaired renal function, route of administration, cranial irradiation, previous sensorineural hearing loss, age under five years, concomitant use of ototoxic drugs, genetic susceptibility, and tumor localization (16). The study aimed to evaluate ototoxicity after MNTI chemotherapy from a long-term perspective.

Case study

This case study presents a long-term ototoxic effects after chemotherapy with cisplatin, vincristine, cyclophosphamide, teniposide and adriamycin in a 10-year-old female patient, who was administered this combination of drugs before and after surgical removal of MNTI at the age of 8 months. A female patient aged three months was admitted to the Department of Haematology and Paediatric Oncology of the Karol Jonscher Clinical Hospital in Poznań with a mixed mesenchymal-neuroectodermal MNTI, a solid tumor within the alveolar ridge. Histopathological examination...
confirmed MNTI. General tests were performed: Morphology, biochemistry, and immunochemistry, which did not show any abnormalities. Diagnostic imaging examinations, which consisted of a chest X-ray and abdominal ultrasound, were also standard. A computed tomography head scan showed lytic and osteogenic bone lesions on the left side. The lytic lesion was 26x15 mm in size and was located within the alveolar ridge of the maxilla. The osteogenic lesions were found in the body of the maxilla near the nasal wings. ‘Floating teeth’ (incisors) were visible within the soft tissues of the alveolar ridge. It was decided to administer chemotherapy before tumor resection. Chemotherapy according to the CWS protocol for standard risk rhabdomyosarcoma, which consisted of 7 treatments with vincristine and dactinomycin, was distributed. Before the introduction of chemotherapy, the patient underwent a hearing examination. Due to the patient’s age and her apparent lack of cooperation, a non-invasive, objective hearing test was performed, namely a 3/5 otoacoustic emissions (OAEs) screening test. This test makes it possible to detect hearing loss of cochlear origin and to assess the function of external hair cells. It involves the recording of a very quiet acoustic signal that arises in the cochlea due to the contraction of outer auditory cells. For both ears, responses for all the frequencies were recorded, which means that the acoustic cell responded to the two-tone stimuli (Table I).

At the age of 8 months, the patient underwent surgical removal of the tumor in the Department of Oncological Surgery for Children at the Institute of Mother and Child in Warsaw. The removed fragment of the maxillary bone was 2.5x1.4x1.5 cm in size, was covered by overlying mucosa, and contained pieces of tooth structure. Next, multidrug chemotherapy was introduced with 23.5 mg cisplatin, 95 mg cyclophosphamide, 9.5 mg adriamycin, and 23.5 mg teniposide injected intravenously. One year after the completion of chemotherapy, another 3/5 otoacoustic emissions (OAEs) screening test was performed. The results for the left and right ears were normal (Table II).

At the age of 8 years (Fig. 1) the girl came for consultation to the Clinic of Maxillofacial Orthopaedics and Orthodontics at the University of Medical Sciences in Poznań, of which she has been a patient ever since. To improve the aesthetics and function of the masticatory apparatus after the resection procedure, orthodontic treatment was planned and implemented. There were no changes in the structures of soft and bone tissues other than those connected with post-operative healing. After two years, as part of the orthodontic treatment, the patient was referred to the Department of Hearing Healthcare Profession, Chair of Biophysics Poznan University of Medical Sciences, Poland for a hearing test. Otoscopic examination revealed no contraindications for performing...
the audiological evaluation. Subjective tests were conducted using a Madsen Ite II diagnostic audiometer and included pure-tone audiometry for the extended frequency range from 125 Hz to 16 kHz and speech audiometry. In accordance with the cross-check principle, objective tests were also performed: Classic tympanometry for the 226 Hz frequency; wideband tympanometry for the frequency range 226-8,000 Hz; stapedial reflex assessment with a Titan tympanometer (Interacoustic); and a Distortion Product Otoacoustic Emissions (DPOAE) test using a Madsen Capella 2 device (Medicus). Otoacoustic emissions evaluation makes it possible to measure the activity of external auditory cells; in particular, the DPOAE test indicates the frequency ranges in which external auditory cells are affected by platinum compounds.

The tests yielded the following results: Otoacoustic emissions were correct in both ears, normal tympanograms were obtained for both the right and left ear (type A), with correct stapedial muscle reflexes for all frequencies (Figs. 2 and 3; Table III). Absorbance measurements for both ears revealed characteristic peaks at around 1,000 and 3,000 Hz. The hearing threshold determined for the frequencies of 500, 1,000, 2,000, and 4,000 Hz was five dBHL for the right ear, and ten dBHL for the left ear (Fig. 4). Speech audiometry results were consistent with the results of pure-tone audiometry: The Speech Reception Threshold (SRT) was 35 dBSPL for both ears. However, a significant increase in the hearing threshold of both ears was recorded for the frequency range between 6,000 and 16,000 Hz. The results obtained reveal substantial abnormalities.

The present study was reviewed and approved by the institutional ethics committee of Poznan University of Medical Sciences. All the procedures performed in studies...
Table III. Results of distortion product otoacoustic emissions tests for the right and left ear, 10 years after chemotherapy.

| F2 (Hz) R/L | GM (dB) R/L | 11/12 R/L | DP1 (dB) R/L | NF (dB) R/L | SNR (dB) R/L | Result R/L    |
|-------------|------------|-----------|--------------|-------------|--------------|---------------|
| 498/498     | 452/452    | 64/55/64/55 | 14/20        | 9/23        | 5/-2         | Rejected/Rejected |
| 596/596     | 539/539    | 64/54/64/54 | 30/18        | 24/22       | 7/-4         | Pass/Rejected  |
| 703/703     | 636/636    | 64/54/64/54 | 17/12        | 11/16       | 6/-4         | Rejected/Rejected |
| 840/840     | 763/763    | 64/55/64/54 | 14/23        | 0/15        | 14/7         | Pass/Pass     |
| 996/996     | 904/904    | 64/55/64/54 | 19/23        | -5/17       | 23/7         | Pass/Pass     |
| 1191/1191   | 1079/1079  | 64/54/64/54 | 20/22        | -2/-2       | 22/25        | Pass/Pass     |
| 1416/1416   | 1283/1283  | 65/55/64/51 | 22/20        | -11/2       | 33/18        | Pass/Pass     |
| 1680/1680   | 1521/1521  | 65/55/68/57 | 20/20        | 7/-5        | 14/26        | Pass/Pass     |
| 2002/2002   | 1812/1812  | 65/54/65/54 | 20/19        | 7/8         | 14/11        | Pass/Pass     |
| 2383/2383   | 2157/2157  | 65/55/65/55 | 16/19        | -14/1       | 30/18        | Pass/Pass     |
| 2832/2832   | 2560/2560  | 65/55/65/55 | 16/12        | 0/-9        | 15/21        | Pass/Pass     |
| 3359/3359   | 3042/3042  | 65/55/65/55 | 12/9         | -15/-12     | 27/21        | Pass/Pass     |
| 4004/4004   | 3625/3625  | 65/55/65/55 | 7/-2         | -18/-9      | 25/7         | Pass/Pass     |
| 4756/4756   | 4305/4305  | 65/5464/55 | 8/-1         | -11/-12     | 18/11        | Pass/Pass     |
| 5654/5654   | 5121/5121  | 65/55/65/55 | 5/7          | -14/-9      | 19/16        | Pass/Pass     |
| 6729/6729   | 6093/6093  | 63/53/63/54 | -14/-5       | -16/-15     | 3/10         | Rejected/Pass |
| 7998/7998   | 7239/7239  | 63/55/63/55 | 5/9          | -10/-5      | 15/15        | Pass/Pass     |

R, right ear; L, left ear; F, frequency; GM, geometric mean; l, level; DP, distortion product; NF, noise floor; SNR, signal to noise ratio.

Figure 4. Results of pure-tone audiometry for each ear, 10 years after chemotherapy.

Involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards (no. 645/16). Written informed consent was obtained from all parents prior to enrollment.

Discussion

Platinum compounds are used in the standard treatment of mesenchymal-neuroectodermal tumors in pediatric oncology. The use of cisplatin is one of the most common causes of drug-induced hearing loss because its ototoxicity has a
destructive effect on external auditory cells, which are not capable of regeneration (18). The means that the hearing loss after cisplatin-based treatment is irreversible (19). In this study, a patient with a mesenchymal-neuroectodermal tumor who had been treated with cisplatin was diagnosed with bilateral high-frequency hearing loss, which is consistent with literature reports (10-13). The damage associated with chemotherapy begins in the first row of the external auditory cells, at the base of the cochlea, where high-frequency sounds are processed. As a result, chemotherapy using cisplatin causes bilateral high-frequency sensorineural hearing loss, which is consistent with our findings (20). High frequencies are not crucial for the understanding of speech; however, with higher doses and the passage of time after the completion of the treatment, hearing loss may in some cases also affect lower frequencies (21).

As a consequence, cisplatin-induced ototoxicity can impair a child's development, learning, and behavior (12,22). Unfortunately, in our case no previous pure-tone audiometry tests were performed, which makes it impossible to determine whether the hearing loss is progressive or whether it has remained at the same level since the end of chemotherapy. In the literature, reports are stating that after the completion of treating hearing loss is permanent and stable (19,23). However, many authors have observed progressive hearing loss following chemotherapy with platinum compounds in children treated for solid tumors (15,21,22).

It is worth noting the research of Liberman et al., conducted on a group of 200 patients to assess hearing loss caused by cancer treatment in childhood. The types of cancer from which the studied patients suffered included solid tumors. All the patients were seen at least eight years after the cancer treatment, which consisted of a combination of radiotherapy and chemotherapy with or without the use of cisplatin (CDDP). The audiological evaluation included pure-tone audiometry, speech audiometry, and impedance audiometry. The assessment of hearing loss was made according to the criteria adopted by the International Office for Audiophonology, where a hearing loss means the presence of pure tones >20 dBHL for the frequency range 500-4,000 Hz. The authors found symmetric, bilateral hearing loss at the 4, 6 and 8 kHz frequencies in patients who had undergone chemotherapy with CDDP, and in those after radiotherapy combined with chemotherapy using CDDP. Hearing loss was not observed in patients who had experienced only radiotherapy or chemotherapy without CDDP. It was found that the risk factors for hearing loss are the use of CDDP in cancer therapy and the patient's age at the time of cancer diagnosis (24). Evaluation of the patient discussed in this paper conducted ten years after the completion of chemotherapy clearly shows a high-frequency hearing loss, which is consistent with the foregoing study. Cooperation with the child's parents/guardians is essential. Their consent and help in the multi-faceted therapy of the child (regardless of the disease entity) is a prerequisite for the implementation of treatment and rehabilitation procedures, which was emphasized in many items cited, including the study, references.

Most of the available literature does not contain reports on the possibility of complications resulting from the administration of cisplatin-based chemotherapy in the treatment of MNTI. One of the possible side effects of cisplatin is ototoxicity, which developed in the patient discussed in this paper, an occurrence which is confirmed by literature reports. Cisplatin-induced hearing loss develops in patients in the long-term and initially affects only the high-frequency range. In the presented case, hearing loss was observed ten years after the completion of chemotherapy, and it concerned high frequencies in the 6,000 to 16,000 Hz range for both ears. Thus, it is essential to inform the parents or legal guardians of a child patient in advance about the possibility of ototoxicity and to acquaint them with the possible consequences of hearing the loss in children. It is also crucial to ensure multidisciplinary cooperation between doctors and hearing care professionals monitor the auditory system during and after chemotherapy.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

DHJ conceived the current study, developed the methodology, supervised the experiments and critically revised the manuscript. ACh and ACz analyzed and interpreted orthodontic treatment data, and analyzed orthodontics literature. ACh edited the figures and wrote the manuscript. MMK carried out orthodontic treatment, collected data, was responsible for patient approval and secured intellectual property from the patient and parents. AM and MUO analyzed and interpreted hearing system data. AM analyzed ototoxicity literature. MUO carried out audiological examination and wrote the manuscript. TMB conceived and scheduled the experiments, interpreted results, edited and revised the manuscript, and approved the final version of the manuscript for publication. All authors read and approved the final manuscript.

Ethics and consent to participate

The present study was reviewed and approved by the Institutional Ethics Committee of Poznan University of Medical Sciences. All the procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards (no. 645/16). Written informed consent was obtained from all parents prior to enrollment.

Patient consent for publication

Parents provided written informed consent for the publication of any associated data and accompanying images.
Competing interests

The authors declare that they have no competing interests.

References

1. Chaudhary S, Manuja N, Ravishankar CT, Sinha A, Vijayran M and Singh M: Oral melanotic neuroectodermal tumor of infancy. J Indian Soc Pedod Prev Dent 32: 71-73, 2014.
2. Andrade NN, Mathai PC, Sahu V, Aggarwal N and Andrade T: Melanotic neuroectodermal tumour of infancy-A rare entity. J Oral Biol Craniofac Res 6: 237-240, 2016.
3. Neven J, Hulsbergen-van der Kaa C, Groot-Loonen J, de Wilde PC and Merkx MA: Rucurrent melanotic neuroectodermal tumor of infancy: A proposal for treatment protocol with surgery and adjuvant chemotherapy. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 106: 493-496, 2008.
4. Ubale P, Baldwa N and Gujar P: Anaesthetic management of a neuroectodermal tumor of infancy: A rare case report. Anaesth Essays Res 11: 251-253, 2017.
5. Łyskawa W: Chemiotherapy in the neoplasmatic diseases treat-ment and its neurotoxicity. Anestezjol i Ratow 3: 80-87, 2009.
6. Karasawa T and Steyger PS: An integrated view of cisplatin-induced nephrotoxicity and ototoxicity. Toxicol Lett 237: 219-227, 2015.
7. İşık A, Grassi A and Soran A: Positive axilla in breast cancer; clinical practice in 2018. Eur J Breast Health 14: 134-135, 2018.
8. Isik A, Karavas E and Firat D: Spontaneous milk fistula from an axillary accessory breast. Breast J 25: 154, 2019.
9. Olgı un Y, A k t a ş S, A lt u n Z, K ı rk ı m G, K ı z ma şlu D Ç, E r ç et i n A P, Demir B, İnce D, Mutafoğlu K, Demirağ B, et al: Analysis of genetic and non genetic risk factors for cisplatin ototoxicity in pediatric patients. Int J Pediatr Otornolaryngol 90: 64-69, 2016.
10. Breglio AM, Rusheen AE, Shide ED, Fernandez KA, Spielbauer KK, McLachlin KM, Hall MD, Amable L and Cunningham LL: Cisplatin is retained in the cochlea indefinitely following chemotherapy. Nat Commun 8: 1654, 2017.
11. Einarsrud EJ, Petersen H, Wiebe T, Fransson PA, Gremner J, Magnusson M and Moëll C: Long term hearing degeneration after platinum-based chemotherapy in childhood. Int J Audiol 49: 765-771, 2010.
12. Dean JB, Hayashi SS, Albert CM, King AA, Karzon R and Hayashi RJ: Hearing loss in pediatric oncology patients receiving carboplatin-containing regimens. J Pediatr Hematol Oncol 30: 130-134, 2008.
13. Sheht S, Mukherjea D, Rybak LP and Ramkumar V: Mechanisms of cisplatin-induced ototoxicity and otoprotection. Front Cell Neurosci 11: 338, 2017.
14. Clemens E, de Vries AC, Pluim SF, Am Zehnhoff-Dincessen A, Tissing WJ, Loonen JJ, van Dulmen-den Broeder E, Bresters D, Versluijs B, Kremer LC, et al: Determinants of ototoxicity in 451 platinum-treated Dutch survivors of childhood cancer: A DCOG late-effects study. Eur J Cancer 69: 77-85, 2016.
15. Bertolini P, Lassalle M, Mercier G, Raquin MA, Izzì G, Corradini N and Hartmann O: Platinum compound-related ototoxicity in children: Long-term follow-up reveals continuous worsening of hearing loss. J Pediatr Hematol Oncol 26: 649-655, 2004.
16. Bess FH, Dodd-Murphy J and Parker RA: Children with minimal sensorineural hearing loss: Prevalence, educational performance, and functional status. Ear Hear 19: 339-354, 1998.
17. Davis JM, Effenbein J, Schum R and Bentler RA: Effects of mild and moderate hearing impairments on language, educational, and psychosocial behavior of children. J Speech Hear Disord 51: 53-62, 1986.
18. Sergi B, Ferraresi A, Troiani D, Paludetti G and Fetoni AR: Cisplatin ototoxicity in the guinea pig: Vestibular and cochlear damage. Hear Res 182: 56-64, 2003.
19. Clemens E, de Vries AC, Am Zehnhoff-Dincessen A, Tissing WJ, Loonen JJ, Pluim SF, van Dulmen-den Broeder E, Bresters D, Versluijs B, Kremer LC, et al: Hearing loss after platinum treat-ment is irreversible in noncranial irradiated childhood cancer survivors. Pediatr Hematol Oncol 34: 120-129, 2017.
20. Lin CP, Liu JD, Chow JM, Liu CR and Liu HE: Small-molecule c-Myc inhibitor, 10058-F4, inhibits proliferation, downregulates human telomerase reverse transcriptase and enhances chemo-sensitivity in human hepatocellular carcinoma cells. Anticancer Drugs 18: 161-117, 2007.
21. Fetoni AR, Lucidi D, De Corso E, Sergi B, Conti G and Paludetti G: Audiological monitoring in children treated with platinum chemotherapy. Audiol Neurootol 21: 203-211, 2016.
22. Waissbluth S, Chuang A, Del Valle Á and Cordova M: Long term platinum-induced ototoxicity in pediatric patients. Int J Pediatr Ototorhinolaryngol 107: 75-79, 2018.
23. Kushner BH, Budnick A, Kramer K, Modak S and Cheung NK: Ototoxicity from high-dose use of platinum compounds in patients with neuroblastoma. Cancer 107: 417-422, 2006.
24. Liberman PH, Goffi-Gomez MV, Schultz C, Novaes PE and Lopes LF: Audiological profile of patients treated for childhood cancer. Braz J Otorhinolaryngol 82: 623-629, 2016.

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.