Infliximab in Autoimmune Inner Ear Disease: A Case Report

Pauline Millan[1] and Kehinde Sunmboye[2]

[1]University Hospitals of Leicester NHS Trust
[2]University of Leicester

January 09, 2025

Introduction

Autoimmune inner ear disease (AIED) is a condition first described by McCabe in 1979 based on a diagnostic study on a cohort of patients[1] who presented with bilateral sensorineural hearing loss (SNHL) with a specific clinical pattern that did not fit with existing diagnoses and demonstrated audiometric improvement with corticosteroid and immunosuppressive therapy. The pathogenesis of AIED is not completely understood, though several mechanisms have been proposed, including uncontrolled humoral and cell-mediated reactions against inner ear antigens, [2] resulting in autoantibody development and T-cell responses. [3]AIED accounts for <1% of SNHL cases [2]but may be under-diagnosed due to a lack of standardised diagnostic criteria. [4] The main treatment has been corticosteroids; however, the overall reported response is 60-70%[2] and only 14% remain responsive after 34 months. [5] There is a risk of further decline in hearing in the absence of therapy. Alternative immunosuppressive treatments [3] were tried but these have yielded variable results. There is no standard treatment protocol for AIED following corticosteroids as randomised controlled trials are limited.[6] Here, we report a case of AIED in a patient that responded well to infliximab.

Case History/Examination

A 27-year-old man with a history of ulcerative colitis (UC) diagnosed at 19 years old, migraines and childhood asthma presented to the emergency department (ED) with a 2-week history of severe vertigo, vomiting, bilateral hearing loss (left ear worse than the right) and tinnitus. He has a family history of ischaemic heart disease. At the time, the patient was on Azathioprine for his UC and had been on the medication for years but was not in remission. On examination by ENT, he was noted to have left-beating nystagmus and catch-up saccades, and an audiogram showed mild, symmetrical hearing loss (*Figure 1a-1b*). Admission blood tests, including C-reactive protein (CRP), were unremarkable other than a slightly raised neutrophil count (*Table 1*). During his 6-day inpatient admission, an MRI of the head and bilateral internal auditory meatus (IAM) with and without contrast was done, which showed no mass lesion in the cerebellopontine angle or internal auditory canals and no cause could be identified for the patient's symptoms.

Differential Diagnosis

The patient was treated for bilateral labyrinthitis with prednisolone 60mg once daily (OD), tapering the dose by 10mg daily, and his symptoms improved. He was then discharged with a follow-up plan for vestibular rehabilitation and balance clinic.

Less than 2 weeks later, the patient presented to ED again with a relapse of his symptoms. A repeat audiogram showed moderate, symmetrical hearing loss (*Figure 1c*). Routine blood tests showed a mildly raised neutrophil count again but was otherwise unremarkable. Further investigations were conducted, including an autoimmune screen to exclude other systemic autoimmune disease, myeloma screen and Treponemal antibody testing, all of which were negative (*Table 1*). The patient was treated with a second course of high-dose prednisolone 60mg OD and discharged home with an urgent follow-up in Emergency ENT Clinic, where he

was prescribed a further week course of prednisolone 60mg. He was then referred to the Vestibular Rehabilitation Team and Rheumatology for suspected AIED. The patient was started on bilateral intratympanic Solu-Medrone injections by ENT and an 8-week tapering course of prednisolone 40mg OD by Rheumatology. He was also referred to a combined Rheumatology and ENT specialist centre where he received further investigations that confirmed the diagnosis as AIED. This included cortical evoked response audiometry which showed that both ears have mid-frequency hearing loss of around 60dB and higher frequency hearing loss of over 100dB.

Conclusion and Results (Outcome and Follow-Up)

Over the span of 2.5 years, the patient received multiple intratympanic steroid injections and prolonged tapering courses of high-dose prednisolone. *Figure 2* shows a summary of the treatments he received and highlights the extensive number of steroid courses he had. It was also noted that the patient would no longer respond to prednisolone 40mg in the later course of his presentation and would see improvement only when 60mg (tapered over 12 weeks) was prescribed (*Figure 3a-3b*). Whilst clinical and audiometric improvements were noted with steroid therapy, his hearing loss and symptoms would worsen when he was on lower doses or off steroids, with relapses occurring as early as 3 days after discontinuation. This, alongside the fluctuating nature of his symptoms, was very frustrating for him and prompted him to research specialist centres and ask for a second opinion.

The patient's case was discussed in a multidisciplinary team (MDT) meeting by the specialist centre, with an outcome to consider methotrexate or anti-tumour necrosis factor α (anti-TNFα) treatment as steroid-sparing therapy. He was started on methotrexate by the local Rheumatology team, with guidance from Gastroenterology in the management of his UC. He was determined to start anti-TNFα therapy but there were barriers to acquiring this treatment for AIED as it required an individual funding request (IFR) to be funded by the National Health Service (NHS). Unfortunately, the IFR was rejected, which was very upsetting to the patient and his family. The specialist centre MDT advised that AIED is a rare manifestation or complication of UC, so an alternative option was explored to acquire anti-TNFα therapy via this pathway. Despite treatment with azathioprine and multiple high-dose steroid courses, remission had not been achieved for his UC, so his case was discussed in inflammatory bowel disease (IBD) MDT and was approved to start treatment with infliximab.

The patient was commenced on infliximab infusions 2.5 years after his initial presentation. He reported that his hearing has remained stable after two loading doses of infliximab (*Figure 3c*), along with improvement in his bowel habits and symptoms of UC. The infliximab is well-tolerated, though the patient initially complained of non-specific elbow and wrist pain with no associated morning stiffness or swelling three months into the treatment, when approaching the next infliximab dose. He also reported an area of numbness on the left thigh above the superolateral aspect of knee that has persisted since starting the first infliximab infusion. Considering the nature of this numbness and his background of sitting for prolonged periods of time for his office job, this was thought to be meralgia paraesthetica. Nerve conduction studies were requested to exclude other causes. After a 24-month follow-up with audiograms, the patient's hearing remained stable, his UC is in remission, and he has not required further courses of steroids.

Discussion

AIED is a rare cause of bilateral SNHL, accounting for <1% of cases, with a yearly incidence of <5 per 100 000.[2] It was described by McCabe in 1979 following a case series involving 18 patients who presented with bilateral SNHL (>30 dB for at least 3 frequencies) that showed clinical and audiometric improvement to immunosuppressive therapy, with no clear cause. [1, 4] The hearing loss in AIED is characterised by its bilateral, asymmetric and fluctuating nature.[6,7] Patients can also report tinnitus and ear fullness (25-50%), and vestibular symptoms such as disequilibrium, ataxia, nystagmus and episodic or positional vertigo (50%).[2, 7] It has a rapidly progressive onset, developing between 3 to 90 days.

The pathogenesis is not completely understood and studies on AIED have been difficult due to (1) the limited anatomical access to the cochlea, (2) unreliable data from peripheral blood immune system and (3) a lack of

an ideal animal model. [5] The proposed mechanism for AIED is thought to be an uncontrolled, combined humoral and cell-mediated reaction against inner ear antigens[2, 3] which promotes autoantibody formation and pro-inflammatory T-cell responses. This results in: (1) cochlear vascular injury due to immune complex deposition, (2) autoantibody-related microthrombosis and (3) vascular changes involving electrochemical disturbances and impaired neurosignalling.[2]

When the inner ear is the only organ affected, AIED is considered 'primary'. If it occurs with systemic autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis and Sjogren's syndrome, it is considered 'secondary'. Secondary AIED accounts for up to 30% of cases. [2] The Harris AIED classification [7] further categorises the condition into 6 different types. Our patient's condition co-exists with UC and is classified as secondary AIED, or 'type 2: rapidly progressive bilateral SNHL with systemic autoimmune disease.'[7]

There is a lack of standardised diagnostic criteria and pathognomonic tests for AIED so diagnosis can be challenging and is often based on exclusion. Diagnosis typically relies on 3 factors: clinical evaluation, blood tests and response to corticosteroids. [2, 7] Laboratory tests must be conducted in all patients with suspected AIED. This includes routine blood tests and autoimmune screening (Figure 1) to investigate for underlying systemic autoimmune disease and exclude other differential diagnoses. [2] There are no confirmed serological markers, but a few have been proposed such as heat shock protein 70 (HSP70) antibody, an autoantibody that targets an inner ear antigen. [8] It was thought to be a predictor of steroid responsiveness but in a further study, it was found to be insufficiently sensitive to detect AIED and lacked specificity to predict steroid responsiveness. [5, 7] A response to corticosteroids is defined as meeting these 2 requirements: (1) improvement in SNHL >15 dB at any frequency OR >10 dB in at least 2 consecutive frequencies OR an increase in pure-tone air conduction threshold loss at any frequency or decrease in WRS. [2, 7] MRI also plays a role in the diagnosis to rule out retrocochlear pathologies. [2]

The clinical features of AIED can mimic other inner ear pathologies such as sudden sensorineural hearing loss (SSHL) and Meniere's disease (MD),[2, 8] and may often be misdiagnosed. It can be differentiated by observing the timing of disease onset; for example, hearing loss in SSHL is characterised by an acute onset of <3 days and in MD, this typically occurs over years.[2] A case report by Ho et al. [2016] discussed a patient with AIED presenting as MD [8]who, after 4 years of symptom onset, presented with psoriasis, joint pains and anterior uveitis. It was then that a diagnosis of AIED was suspected. The patient was started on a trial of corticosteroids, which he responded to, and was switched to steroid-sparing therapy.[9] In our patient's case, he was initially diagnosed with bilateral labyrinthitis following his unremarkable MRI and blood test results. The diagnosis of AIED was considered approximately 5 weeks after his initial presentation after he re-presented multiple times with a deterioration in his hearing shortly after finishing his course of steroids. However, it took almost 1 year from his initial presentation and referral to an ENT specialist that undertook cortical evoked response audiometry to definitively confirm the diagnosis of AIED.

AIED is one of the few forms of SNHL which may be reversible so prompt medical management is crucial as it may improve the rates of reversing hearing loss. [4] The patients in McCabe's study in 1979 were initially treated with cyclophosphamide and corticosteroids[1] however due to the substantial risks associated with long-term cyclophosphamide use, including malignancy and myelosuppression, most clinicians favoured high-dose prednisolone (60mg OD) as the primary treatment for AIED. [6]High-dose steroid use is also associated with health risks and adverse effects [6] such as hyperglycaemia, weight gain and fractures secondary to osteoporosis. A study found that with good patient education and monitoring, it is a safe and effective treatment for AIED [10] but is not effective for long-lasting management and is associated with episodes of relapse.[11]

Although corticosteroids remain the mainstay treatment, there are varying levels of steroid-responsiveness initially and throughout the treatment. One study evaluating the efficacy of AIED treatment reported that the overall patient response rate to oral prednisolone was 69.7%.[6, 7] Another study found that only 14% remain corticosteroid-responsive after 34 months, most notably in those who present with repetitive deterioration in hearing requiring corticosteroid treatment. [6] Our patient received numerous courses of

steroids during this treatment process and initially saw an improvement in his symptoms with prednisolone 40mg OD later required 60mg OD to get the same response. He would also experience a worsening of his symptoms when he is on lower doses or off steroids, relapsing as early as 3 days after stopping treatment.

There is a risk of further decline in hearing in the absence of therapy and yet, there is no standard treatment protocol for AIED following corticosteroids as randomised controlled trials (RCTs) are limited.[7] Studies regarding alternative steroid-sparing therapies have yielded variable results, with much of the data relying on case reports and case series. [3, 11]Alternative therapies that have been trialled include methotrexate, azathioprine and immunomodulators [11] such as biologics, including TNFα inhibitors (etanercept and infliximab), CD20 inhibitors (rituximab) and IL-1 inhibitors (anakinra and canakinumab). If medical treatment fails and hearing is lost, cochlear implantation is an effective treatment option for these patients.[4]

The efficacy of methotrexate was assessed in a multicentre clinical trial as a potential steroid sparing therapy in corticosteroid-responsive patients but did not demonstrate a greater effect than the placebo. [5] A case report described a presentation of relapsing AIED in a 35-year-old woman who had a significant response to methotrexate and azathioprine dual therapy. This combination yielded positive outcomes and was well-tolerated. [12] Our patient was initially tried on methotrexate in combination with azathioprine which he was already taking for his UC but unfortunately showed little to no improvement.

Our patient's AIED is classified as secondary and more specifically, it fits the Harris AIED classification type 2 that often worsens with flare of the autoimmune condition. This type is steroid-responsive and can be managed with targeted therapies that are effective against their underlying condition. [7] The AIED specialist centre and gastroenterology agreed that AIED is a rare manifestation or complication of UC. This, combined with the failure of achieving remission for his UC despite being on azathioprine and receiving multiple courses of high-dose steroids, led the MDT to commence him on infliximab. The patient showed clinical and audiometric improvement after two loading doses of infliximab infusions. His hearing remained stable, and he also reported improvement in his bowel habits and symptoms of UC since starting therapy. The patient has tolerated infliximab well and has remained on the infusions.

On literature review, there are two similar case reports to our patient's presentation. One reported a case of a 49-year-old man with AIED who was responsive to corticosteroids but experienced frequent relapses and progressive deterioration of hearing. He was tried on multiple agents, but these failed to stabilise his symptoms. After receiving infliximab treatment, he was noted to have a sustained improve in his hearing and tinnitus. There was an attempt to discontinue his treatment after 46 weeks, but this led to a rapid relapse of his condition, though his hearing quickly recovered after restarting infliximab. [13] Another case report presented a case of AIED in a patient with Crohn's disease that showed improvement to anti-TNFα therapy, halting the progression of hearing loss, as well as improving hearing by an average of 15dB across all frequencies. The patient's hearing remained stable after. [14]

A pilot placebo-controlled study on anti-TNFα therapy, etanercept, in AIED however resulted in a different outcome. [15]This involved 20 patients with AIED in a 12-week blinded placebo-controlled RCT of subcutaneous etanercept 25mg twice weekly. The efficacy of etanercept therapy failed to exceed the placebo response. Another study on 8 patients with steroid-refractory AIED concluded that systemic infliximab therapy did not improve hearing loss.[16]

Although studies on biologic therapy have variable results on hearing improvement, they have shown benefits on treating other aural symptoms such as ear fullness, vertigo and tinnitus, [8]with a retrospective study reporting that >80% of patients demonstrated improvement in these symptoms on treatment with adalimumab and rituximab. [7] Some studies involving methotrexate have also demonstrated a similar result, with one reporting an 80-100% improvement rate in vestibular symptoms.[9] Steroid-sparing therapy should therefore not be eliminated based on lack of improvement in hearing alone.

The disparity in response could potentially be explained by factors such as timing of the treatment relative to corticosteroid use, the type of anti-TNFα therapy used, and route of administration.[5] The later adaptive immune responses in AIED are often influenced by the early expression of cytokines during the innate immune

response, such as TNF. Elevated levels of TNF are identified to be predictive of corticosteroid-responsiveness in AIED. Experimental observations reveal that peripheral blood immune cells from corticosteroid-responsive patients release high levels of TNF in vitro and these are reduced significantly on administration of dexamethasone. It is possible that the initial use of corticosteroids prior to anti-TNFα administration causes an excessive reduction of the TNF levels, potentially compromising its effectiveness in placebo-controlled trials. [5]

Conclusion

AIED is one of the few forms of SNHL for which a treatment is available therefore early diagnosis and intervention is important. We report a case of secondary AIED in patient with a significant response to infliximab therapy. Studies on the use of anti-TNFα therapy for AIED as a steroid-sparing alternative are limited and showed variable results. To assess and establish the efficacy of anti-TNFα therapy in the management of AIED, large multicentre randomised controlled trials are required that measure not only improvement in hearing but also other aural symptoms. This, however, may be difficult due to the rarity of the condition and the lack of a standardised diagnostic criteria.

Author Contributions

Pauline Millan: Data curation, Project administration, Resources, Software, Writing - original draft.

Kehinde O. Sunmboye: Conceptualisation, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Writing - original draft, Writing - review and editing.

Informed consent

Written informed consent was obtained from the patient for the publication of this case report.

Data availability

The data used to support the findings of this case report are available from the author upon request.

Conflict of Interest

The authors declare that they have no conflicts of interest.

References

1. McCabe, B. F. 1979. "Autoimmune Sensorineural Hearing Loss." *Annals of Otology, Rhinology & Laryngology 88* (5): 585–89. https://doi.org/10.1177/000348947908800501.

2. Ciorba, A., Corazzi V., Bianchini C., Aimoni, C., Pelucchi S., Skarżyński, P. H., and Hatzopoulos, S. 2018. "Autoimmune Inner Ear Disease (AIED): A Diagnostic Challenge." *International Journal of Immunopathology and Pharmacology* 32 (March): 205873841880868. https://doi.org/10.1177/2058738418808680.

3. Shamriz, O., Tal Y., and Gross, M. 2018. "Autoimmune Inner Ear Disease: Immune Biomarkers, Audiovestibular Aspects, and Therapeutic Modalities of Cogan's Syndrome." *Journal of Immunology Research* 2018 (April): 1498640. https://doi.org/10.1155/2018/1498640.

4. Oz, R. S., Gluth, M., and Tesher, M. S. 2019. "Pediatric Autoimmune Inner Ear Disease: A Rare, but Treatable Condition." *Pediatric Annals* 48 (10). https://doi.org/10.3928/19382359-20190923-01.

5. Vambutas, A., and Pathak, S. 2016. "AAO: Autoimmune and Autoinflammatory (Disease) in Otology: What Is New in Immune-Mediated Hearing Loss." *Laryngoscope Investigative Otolaryngology* 1 (5): 110–15. https://doi.org/10.1002/lio2.28.

6. Strum, D., Kim S., Shim, T., and Monfared, A. 2020. "An Update on Autoimmune Inner Ear Disease: A Systematic Review of Pharmacotherapy." *American Journal of Otolaryngology* 41 (1): 102310. https://doi.org/10.1016/j.amjoto.2019.102310.

7. Matsuoka, A. J., and Harris, J. P. 2013. "Autoimmune Inner Ear Disease: A Retrospective Review of Forty-Seven Patients." *Audiology and Neuro-Otology* 18 (4): 228–39. https://doi.org/10.1159/000351289.

8. Sakano, H., and Harris, J. P. 2018. "Emerging Options in Immune-Mediated Hearing Loss." Laryngoscope Investigative Otolaryngology 4 (1): 102–8. https://doi.org/10.1002/lio2.205.

9. Ho, E. C., and Yao, G. L. 2016. "Autoimmune Inner Ear Disease Presenting as Menière's Disease." *The Journal of Laryngology & Otology* 130 (S3): S175–75. https://doi.org/10.1017/s0022215116005569.

10. Alexander, T. H., Weisman, M. H., Derebery, J. M., Espeland, M. A., Gantz, B. J., Gulya, A. J., Hammerschlag, P.E., et al. 2009. "Safety of High-Dose Corticosteroids for the Treatment of Autoimmune Inner Ear Disease." *Otology & Neurotology* 30 (4): 443. https://doi.org/10.1097/MAO.0b013e3181a52773.

11. Balouch, B., Meehan, R., Suresh, A., Zaheer, H.A., Jabir, A. R., Qatanani, A. M., Suresh, V., Kaleem, S. Z., and McKinnon, B. J. 2022. "Use of Biologics for Treatment of Autoimmune Inner Ear Disease." *American Journal of Otolaryngology* 43 (5): 103576–76. https://doi.org/10.1016/j.amjoto.2022.103576.

12. Huang, K. L., Lin, H. C., Lin, C. D., and Wu, P. C. 2023. "Relapsing Autoimmune Inner Ear Disease with Significant Response to Methotrexate and Azathioprine Combination Therapy: A Case Report and Mini Literature Review." *Medicine* 102 (23): e33889–89. https://doi.org/10.1097/md.0000000000033889.

13. Heywood, R. L., Hadavi, S., Donnelly, S., and Patel, N. 2013. "Infliximab for Autoimmune Inner Ear Disease: Case Report and Literature Review." *The Journal of Laryngology & Otology* 127 (11): 1145–47. https://doi.org/10.1017/s002221511300217x.

14. Staecker, H., and Lefebvre P. P. 2002. "Autoimmune Sensorineural Hearing Loss Improved by Tumor Necrosis Factor-α Blockade: A Case Report." *Acta Oto-Laryngologica* 122 (6): 684–87. https://doi.org/10.1080/000164802320396402.

15. Cohen, S., Shoup, A., Weisman, M. H., and Harris, J. 2005. "Etanercept Treatment for Autoimmune Inner Ear Disease: Results of a Pilot Placebo-Controlled Study." *Otology & Neurotology* 26 (5): 903–7. https://doi.org/10.1097/01.mao.0000185082.28598.87.

16. Pathak, S., Goldofsky, E., Vivas, E., Bonagura, V.R., and Vambutas, A. 2011. "IL-1β Is Overexpressed and Aberrantly Regulated in Corticosteroid Nonresponders with Autoimmune Inner Ear Disease." *Journal of Immunology* 186 (3): 1870–79. https://doi.org/10.4049/jimmunol.1002275.

Tables

Test	1st ED Presentation	2nd ED Presentation
WBC	10.0	10.7
Hb	1.66	160
Platelets	324	291
Neutrophils	8.39	9.21
Lymphocytes	1.02	1.00
Sodium	139	140
Potassium	3.6	4.5
Urea	7.4	6.6
Creatinine	85	81
eGFR	>90	>90
Albumin	52	51
ALP	85	68
ALT	19	40
Bilirubin	18	9
Amylase	21	
CRP	<5	15

Test	1st ED Presentation	2nd ED Presentation
HbA1c		30
TSH		1.4
Adjusted calcium		2.20
Phosphate		1.05
Magnesium		0.89
Myeloma screen	Negative	
Treponemal antibody	Not detected	
C3		1.50
C4		0.30
Rheumatoid factor		10
ANA titer		Negative
ANCA (immunofluorescence)		P-ANCA 1:40
MPO-ANCA (chemiluminescence)		3.9
PR3-ANCA (chemiluminescence		1.1
ACE		23
Anti-CCP		1

Figures