Unusual association of diseases/symptoms

An unusual cause of hearing loss in an 81-year-old man

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An 81-year-old man presented to accident and emergency with a recent history of rapidly progressive bilateral hearing loss. Further questioning revealed recent sinusitis, fevers and general malaise. Initial bloods showed raised inflammatory markers, raised creatinine, low albumin and urine dip was positive for blood and protein. Chest x-ray showed faint bilateral mid-zone infiltrates. He was treated with intravenous methylprednisolone (500 mg×3) for presumed Wegener's granulomatosis which was later confirmed by c-anti-neutrophil cytoplasmic antibodies testing (proteinase-3 positive) and supportive findings on CT chest and sinuses. He was discharged after 10 days in hospital on oral prednisolone and cyclophosphamide. He is continuing treatment and seen regularly in outpatient follow-up. Unfortunately his hearing has not fully recovered and he is awaiting a hearing aid.

BACKGROUND

Wegener's granulomatosis (WG) can present with local airways disease or systemically. It most commonly presents with upper and lower respiratory features but systemic disease can affect almost any system and therefore is something all clinicians should be aware of. Untreated it has a 90% mortality.

Progressive hearing loss in the older is common and usually age-related and irreversible. A sudden onset hearing loss, particularly if associated symptoms should alert clinicians to consider other underlying and potentially reversible pathologies.

CASE PRESENTATION

An 81-year-old gentleman presented to his general practitioner (GP) with a 1 week history of bilaterally reduced hearing progressing rapidly over the next 6 weeks to profound bilateral deafness. Over the same period he reported sinus congestion, feeling generally unwell with weight loss and night sweats.

Liver function tests (LFTs) performed by the GP were abnormal and on the basis of this, with his deteriorating clinical condition he was referred to the on-call medical team.

Additional history revealed no tinnitus or vertigo and no pain or discharge from either ear. He reported no recent cough, chest pain or breathlessness; no musculoskeletal symptoms and no rash or dysuria. He volunteered mild symmetrical alteration of sensation in both feet. He had a medical history of glaucoma, bilateral cataract extraction and a fully excised squamous cell carcinoma of the scalp. He had no personal or family history of auto-immune or other disease. He was allergic to penicillin and was on no regular medication. He was independent and self-caring, living with his wife.

On examination he appeared flushed and sweaty, but was afebrile. He had no rashes. There was conjunctival injection in his left eye consistent with episcleritis. On palpation he was tender around his eyes and sinuses. He was mildly tachycardic, blood pressure 141/91 with a peripheral blood oxygen saturation of 98% on room air. Heart sounds were normal. A few crepitations were noted at the base of the right lung. Abdominal examination was unremarkable. On neurological examination he had mild subjective blunting of pin-prick sensation in both feet and absent ankle jerks. The neurological examination was otherwise normal.

INVESTIGATIONS

Routine bloods showed a normocytic anaemia with a haemoglobin of 11.7 g/dl, white cell count $13.6 \times 10^9/l$, neutrophils $11.2 \times 10^9/l$, platelets $657 \times 10^9/l$, C-reactive protein (CRP) 267 mg/l. LFTs were abnormal with alanine transaminase 180 u/l, alkaline phosphatase 305 u/l, albumin 15 g/l. His creatinine at diagnosis was 113 $\mu\text{mol/l}$.

Urine dipstick was strongly positive for blood and protein but hyaline casts only on microscopy.

Vasculitic screen showed a mild polyclonal hypergammaglobulinaemia. Immunofluorescence showed antineutrophil cytoplasmic antibodies (cANCA) with specificity for proteinase-3 (PR-3) was detected by ELISA at 100 units/ml (normal range $<5.5 \text{ u/ml}$).

Chest x-ray showed patchy bilateral mid-zone infiltrates; his CT chest showed multiple parenchymal nodules and CT sinuses multiple mucosal opacities.

Audiology: Profound bilateral sensorineural hearing loss (figure 1).

No biopsies were taken due to the high titre of PR-3+cANCA supporting the clinical diagnosis of WG.

Figure 1 Pure tone audiogram: sensorineural pattern of hearing loss, profound at high frequencies.

DIFFERENTIAL DIAGNOSIS

Hearing loss:

- ▶ Presbycusis
- ▶ Inflammatory: suppurative labyrinthitis, meningitis, mumps, viral
- ▶ Drug related
- ▶ Auto-immune

WG:

- ▶ Upper respiratory tract infections /pneumonia
- ▶ Lung abscess
- ▶ Malignancy
- ▶ Myeloma, head/neck, lung, lymphoma
- ▶ Vasculitic/autoimmune:
- ▶ Wegner's, systemic lupus erythematosus, polyarteritis, Churg Straus, sarcoidosis
- ▶ Glomerulonephritis/Goodpasture syndrome
- ▶ Infective endocarditis
- ▶ Cocaine abuse

TREATMENT

In the emergency department an immediate oral dose of 40 mg prednisolone was given. The next day this was changed to intravenous methylprednisolone which was given for 3 days. Daily oral cyclophosphamide was started simultaneously. After 3 days of intravenous steroids oral prednisolone was started.

Pamidronate was given to protect from osteoporosis and co-trimoxazole was started as prophylaxis against *Pneumocystis jirovecii* infection which can occur in these patients when immunosuppressed.

He was also referred to ENT who decided biopsy was not necessary, formally assessed his hearing, prescribed a flixonase nasal spray and are continuing to follow him up.

OUTCOME AND FOLLOW-UP

After 10 days as an inpatient he made a very good symptomatic response to immunosuppression and his CRP decreased. However, he developed significant renal impairment with his creatinine peaking at 215 u/l 20 days after

diagnosis, before falling back to 117 6 weeks into treatment. He continues to be followed up in rheumatology out-patients.

He is still on cyclophosphamide and oral prednisolone. The cyclophosphamide is likely to be changed to azathioprine shortly, and it is likely that he will remain on this with oral prednisolone for up to 2 years to prevent relapse.

In addition to clinic follow-up he has regular monitoring of his white cells (as leucopenia can be a side effect of cyclophosphamide), and his renal function with regular urine dipstick testing as another side effect is bladder toxicity. As mentioned he takes prophylactic antibiotics as well as a bisphosphonate to combat the effects of long term steroids.

His renal function is improving, unfortunately although he feels his hearing has improved he still has significant hearing impairment and may need hearing aids fitted in the future.

DISCUSSION

WG is a systemic condition characterised by necrotising granulomatous disease of the upper and lower respiratory tracts and a systemic vasculitis affecting small and medium vessels. It is a rare condition with the UK incidence estimated at 8.4/million, prevalence 65/million.¹ The cause is unknown although there is thought to be a genetic predisposition and it has been hypothesised there may be an infective trigger. Almost all patient's with Wegener's are found to have antineutrophil cytoplasmic antibodies (cANCA) with specificity for (PR-3) by ELISA. It is likely that the antibody is pathogenic due to its high sensitivity and specificity, and the fact that titres correlate with disease activity and the condition responds to immunosuppressants. In vitro studies have shown PR3-ANCA can activate primed neutrophils, however animal models demonstrating pathogenicity are still lacking.²

The most commonly affected systems are the upper and lower respiratory tracts; patients often present with sinusitis, epistaxis, cough or haemoptysis. Disease affecting

only the respiratory tract with no systemic involvement is known as 'limited WG'. Renal involvement is seen in approximately 15% at presentation, and is usually first detected as blood and protein on urine dipstick testing, red cell casts seen on microscopy and a rising serum creatinine. By definition disease with renal involvement is 'systemic WG' which is then categorised as severe if the creatinine is $>500 \mu\text{mol/l}$. The vasculitic element of the disease means any organ can be affected. Scleritis, purpura, neuropathy and arthralgia are a few of the wide-ranging symptoms seen either at presentation or later in the disease course.³

Our patient was unusual for two reasons. first his age at presentation was atypical. Although Wegener's can affect patients of any age it is typically seen in 40–60 year olds.⁴ The second unusual feature was that his presenting symptom was sensorineural hearing loss.

A large epidemiological UK-based study estimated the median age for men presenting with WG at 58 with an interquartile range of 48–68. The age specific incidence peaked at 64–74.¹ This finding is supported in other studies.^{3–5}

It is not unusual for Wegener's to present with ENT problems. It is estimated that 25% of patients have a conductive hearing loss secondary to chronic otitis media at presentation. Sensorineural hearing loss is much less common, it is thought to occur due to vasculitis of the small vessels supplying the eighth nerve, the internal auditory artery or its cochlear branch.⁶

Fauci *et al.* undertook a large cohort study in 1983 and estimated that approximately 6% of patients may have a sensorineural hearing loss at presentation. However this study was done before cANCA testing was available and it is possible that these cases were not all in fact Wegener's, suggesting the true rate could be lower.³ Since the introduction of cANCA testing there have been case reports describing sensorineural hearing loss occurring as the presenting symptoms in proven WG, but it is rare.^{7–9}

Pure tone audiograms from our patient showed a profound bilateral sensorineural hearing loss, greater at high frequencies. (figure 1) Although it confirms a sensorineural pattern of hearing loss it is unremarkable. A similar audiogram would be typical of patients with many causes of deafness including presbycusis – hearing loss commonly associated with ageing.

The pathophysiology of presbycusis is not fully understood; the sensory component is thought to be due to atrophy within the organ of corti; and the neural component from atrophy of nerve cells in the cochlea and central neural pathways. The high frequency hearing is lost first as atrophy within the organ of corti originates in the basal turn (high frequency area). Damage progresses over many years towards the apex (low frequency). Therefore this pattern of hearing loss with moderate to severe deafness even at low frequencies could not have been achieved over a period as short as 6 weeks.¹⁰

Early recognition and treatment of WG prevents disease progression and death. Untreated the mortality is estimated at up to 90% with a median survival of 5 months.⁵ The mainstay of treatment is immunosuppression. Currently cyclophosphamide and corticosteroids are usually used to induce remission, followed by prednisolone

and azathioprine or methotrexate as maintenance therapy.¹¹ Patients require follow-up looking for relapse and to monitor adverse reactions to therapy. Hearing loss is often permanent but can improve with therapy in up to half of cases reported.¹² Early treatment (within 1 month on onset of symptoms) improves prognosis.⁸ Unfortunately our patient has not recovered fully from his profound hearing loss and continues to be followed up by the audiologists.

In summary this case illustrates an unusual presentation of a potentially life-threatening inflammatory disease, and highlights the importance of early diagnosis. The case demonstrates the importance of considering vasculitic disorders in any patients, including older patients with no history of auto-immune disease, presenting with hearing loss. Given the natural disease progression of WG it is likely that our patient would have later developed more features of the disease, and been diagnosed as his disease became more established. Further delay in diagnosis would have almost certainly lead to even more significant renal impairment and a worse outcome for his hearing loss.

Learning points

- ▶ WG has a wide range of clinical presentations and can present in the older population
- ▶ Hearing loss is a rare but reported presenting feature
- ▶ cANCA testing is highly specific in diagnosis of WG
- ▶ High mortality untreated
- ▶ Early recognition of WG may reverse hearing loss.

Competing interests None.

Patient consent Obtained.

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