The Journal of Laryngology & Otology (2013), ***127***, *708–711*.

doi:10.1017/S0022215113001047

CLINICAL RECORD

Sudden bilateral sensorineural hearing loss associated with urticarial vasculitis

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Abstract

Background: Bilateral sensorineural hearing loss associated with recurrent urticarial skin lesions may be signs of underlying Muckle–Wells syndrome. Previous reports have described the hearing loss to be progressive in nature.

Method: To our knowledge, this paper presents the first published case of sudden onset, bilateral sensorineural hearing loss associated with urticarial vasculitis due to underlying Muckle–Wells syndrome.

Results: The patient underwent a cochlear implantation with a modest outcome.

Conclusion: Cochlear implantation may help to rehabilitate sudden hearing loss associated with this condition, but early diagnosis may allow treatment with interleukin-1β inhibitors such as anakinra.

Key words: Sensorineural Hearing Loss; Urticaria; Vasculitis; Muckle–Wells Syndrome; Cochlear Implantation; Interleukin

Introduction

Urticarial vasculitis describes a continuum of autoinflammatory dermatological conditions, which may rarely be associated with bilateral sensorineural hearing loss in Muckle–Wells syndrome. The syndrome was first reported in 1962 in a Derbyshire family who presented with a triad of urticarial vasculitis, progressive sensorineural hearing loss and amyloidosis.[1] The diagnostic criteria for Muckle–Wells syndrome have since expanded to include recurrent musculoskeletal symptoms and pyrexia.[2] We present a novel case of sudden bilateral sensorineural hearing loss associated with this condition.

Case report

A 53-year-old male farm labourer presented with severe, sudden onset, bilateral sensorineural hearing loss, a 2-year history of vertigo and an urticarial rash on his lower limbs. For several years he had also been suffering from recurrent episodes of lower limb arthralgia with low grade pyrexia.

Blood tests demonstrated normocytic anaemia, leucocytosis, raised C-reactive protein (30 mg/l) and erythrocyte sedimentation rate (40 mm/h). Renal function testing was normal, as was the autoimmune screening, with normal serum levels of immunoglobulin, complement and rheumatoid factor. Test results for anti-nuclear antibodies and anti-complement antibodies were negative. Serology testing for Lyme disease and human immunodeficiency virus was also negative. The patient was given a two-week course of oral steroids (40 mg prednisolone daily), but his hearing loss failed to improve.

Biopsies of the rash demonstrated cutaneous small vessel leukocytoclastic vasculitis, with features of a type III hypersensitivity reaction and antigen–antibody complex deposition in the vascular lumina. The constellation of otological and dermatological symptoms led to genetic testing, which showed the presence of Q703K missense mutation in the NLRP3 gene on chromosome 1q44, suggestive of underlying Muckle–Wells syndrome. The patient had 14 siblings, all of whom were asymptomatic and declined genetic screening.

The patient was fitted with bilateral digital hearing aids but found them of little help. He was referred to the Auditory Implant Centre at St Thomas' Hospital for cochlear implantation evaluation. Pure tone audiometry revealed profound bilateral sensorineural hearing loss (Figure 1). The patient also complained of left-sided tinnitus and non-rotatory vertigo. Middle-ear function was normal on tympanometry, with absent acoustic reflexes bilaterally. On testing for speech discrimination using the Bamford–Kowal–Bench sentences, the patient scored 0 per cent for both ears using his hearing aids. With lip reading and hearing aids he scored 34 per cent on the left and 0 per cent on the right using the City University of New York sentence test. Auditory brainstem response monitoring was performed wherein both ears were presented with an air conduction click at 100 dBnHL, but no response was detected from either ear.

Computed tomography revealed marked bilateral cochlear and labyrinthine ossification, with some sparing of the basal turn of the left cochlea (Figure 2a). Magnetic resonance imaging demonstrated the loss of signal intensity in both cochleae, but less so in the left (Figure 2b). Following full counselling, the patient opted to receive a left cochlear implant.

Presented orally at the 141st Semon Club meeting, 2 June 2011, London, UK.
Accepted for publication 7 September 2012 First published online 20 May 2013

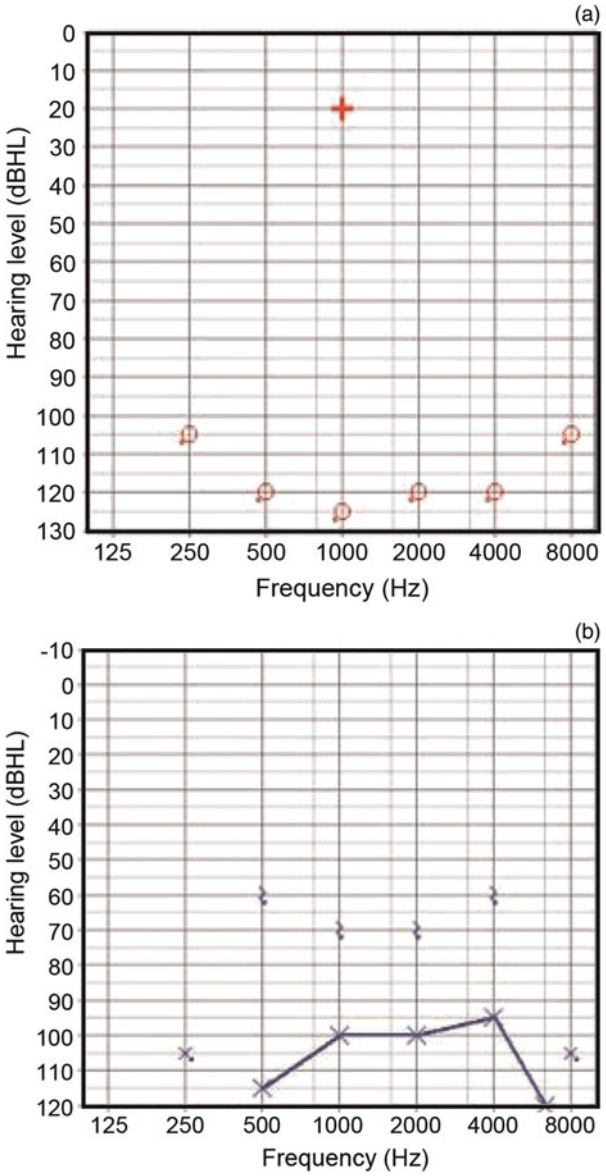

FIG. 1

Patient audiograms of the (a) right and (b) left ears conducted prior to cochlear implantation, showing profound bilateral sensorineural hearing loss.

At surgery, a bony cochleostomy was performed antero-inferior to the round window membrane, allowing complete insertion of the electrode assay into the scala tympani (using the Cochlear Nucleus Freedom 24 implant; Cochlear, Sydney, Australia). The patient recovered well, with no post-operative complications. The cochlear implant was well tolerated and initial rehabilitation was highly encouraging.

Post-implantation, the patient reported utilising the implant full time at work and at home, and was able to converse with his children once more, representing a significant improvement in his quality of life. His tinnitus and balance also improved. Implant-aided sound field testing at 12 months' follow up showed acceptable hearing thresholds (Figure 3). His score on the City University of New York sentence test had risen to 70 per cent, but Bamford–Kowal–Bench speech discrimination scores remained at 0 per cent.

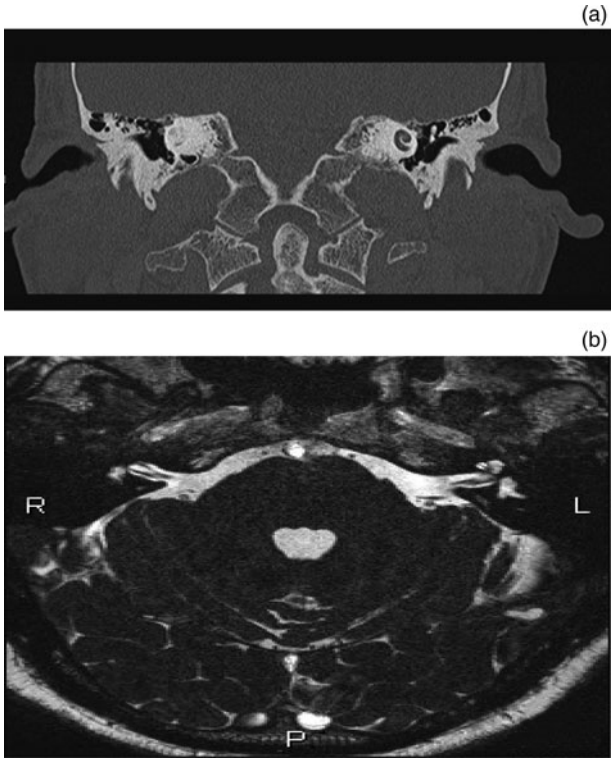

FIG. 2

(a) Coronal computed tomography scan demonstrating right-sided labyrinthine ossification, and (b) axial magnetic resonance (T2-weighted) image showing a loss of signal intensity in the right cochlea. R = right; L = left; P = posterior

Discussion

We believe that our patient is the first reported case of sudden bilateral sensorineural hearing loss associated with urticarial vasculitis, the latter of which encompasses a wide spectrum of autoinflammatory disorders of the skin, including Muckle–Wells syndrome. Patients with this syndrome typically present with recurrent attacks of fever, urticarial rash,

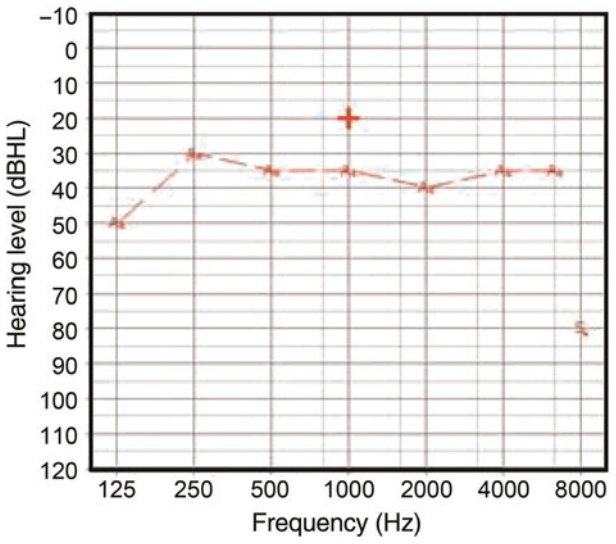

FIG. 3

Patient audiogram of sound field testing following right-sided cochlear implantation.

https://doi.org/10.1017/S0022215113001047 Published online by Cambridge University Press

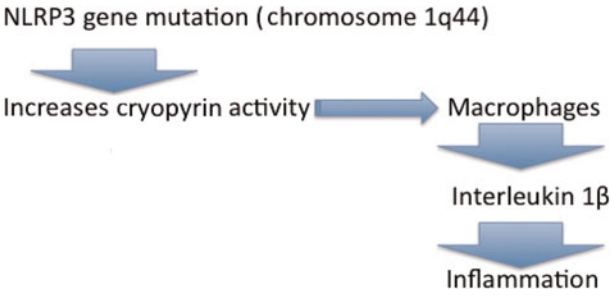

FIG. 4
Pathophysiology of Muckle–Wells syndrome.

arthralgia, arthritis, myalgia and, occasionally, conjunctivitis.[3] Amyloidosis-associated renal disease and sensorineural hearing loss have been reported in more than 50 per cent of cases.

Muckle–Wells syndrome is an extremely rare form of cryopyrin-associated periodic fever syndromes, which are caused by mutations in the NLRP3 (also known as CIAS1) gene on chromosome 1q44.[4] The gene product, cryopyrin, forms part of the inflammasome, multiprotein complex, which is crucial for intracellular host defence.[5] Alterations in cryopyrin lead to excessive macrophage production of the proinflammatory cytokine, interleukin-1β (IL-1β), which leads to uncontrolled inflammation at multiple sites (Figure 4).[5] The hearing loss in Muckle–Wells syndrome is usually bilateral and progressive. However, in our patient, it was of sudden onset and was severe in nature, with continued deterioration in spite of systemic steroid administration. The histological (skin biopsy) findings of antigen–antibody complex deposition in the vascular lumina may have been reflective of a similar pathological process occurring in the cochlea, which led to the patient's sudden sensorineural hearing loss.

Muckle–Wells syndrome is generally inherited in an autosomal dominant manner, but sporadic *de novo* mutations have been reported.[6] The syndrome mutations are typically of the missense type; they are associated with a broad clinical phenotype and variable penetrance. In the case reported here, the patient's genetic test results showed the presence of the Q703K missense change in exon 3 of the NLRP3 gene, which is suggestive of Muckle–Wells syndrome. To date, more than 40 disease-associated mutations have been identified in Muckle–Wells syndrome, including Q703K.[7] It has been debated as to whether Q703K may instead be a polymorphism of the NLRP3 gene;[7] however, Q703K is known to be associated with autoinflammatory conditions involving excess IL-1 production, including Muckle–Wells syndrome.[5] Q703K mutation of the NLRP3 gene also occurs in approximately 22 per cent of patients with the requisite clinical characteristics of Muckle–Wells syndrome, including bilateral sensorineural hearing loss, musculoskeletal symptoms and urticarial skin lesions.[2] Indeed, more than 50 per cent of patients with cryopyrinopathies do not have identifiable disease-associated mutations at all.[7]

Cochlear implantation for profound sensorineural hearing loss associated with urticarial vasculitis, including that of Muckle–Wells syndrome, has not previously been described. In our patient, subjective assessments with implant-aided sound field thresholds and sentence discrimination tests (with aided lip reading) indicated some post-implantation improvement. However, the Bamford–Kowal–Bench speech discrimination scores suggested that the implant was only an adjunct to lip reading. The authors cannot explain the modest post-implantation outcome and can only surmise that the disease may have affected the viability of spiral ganglion cells or auditory neurons in some unknown manner. Retrocochlear involvement has never been reported in Muckle–Wells syndrome.

- **Bilateral sensorineural hearing loss associated with recurrent urticaria should trigger suspicion of Muckle–Wells syndrome**
- **This paper reports a novel case of sudden bilateral sensorineural hearing loss associated with this condition**
- **Cochlear implantation was used to manage sensorineural hearing loss, with a modest outcome**
- **Early recognition of Muckle–Wells syndrome is critical for potential reversal of hearing loss with interleukin-1β inhibitor therapy**

Anakinra is a recombinant IL-1β receptor antagonist, which may halt deterioration of sensorineural hearing loss due to Muckle–Wells syndrome and aid recovery.[8] Anakinra has been associated with near-complete recovery of bilateral moderate sensorineural hearing loss, together with the normalisation of white cell counts and C-reactive protein serum levels.[8] In another study, anakinra therapy was associated with significant improvement in disease activity, including hearing loss improvement two weeks after the commencement of therapy and long-term improvement.[9] It has been suggested that anakinra therapy should be initiated as early as possible to achieve any recovery of hearing loss.[8,9] An earlier diagnosis in our patient might have warranted consideration for treatment with anakinra. In practice, the recognition of an extremely rare and complex condition such as Muckle–Wells syndrome can be challenging, which renders early diagnosis and administration of anakinra therapy difficult.

In conclusion, we wish to highlight that bilateral sensorineural hearing loss associated with recurrent urticaria should trigger suspicion of possible underlying Muckle–Wells syndrome, which is a rare condition that is poorly described in otolaryngological literature. We report a novel case of sudden bilateral sensorineural hearing loss that occurred in association with urticarial vasculitis, likely to be due to Muckle–Wells syndrome, which was managed with cochlear implantation. Early recognition of the disease appears to be the ultimate key, as it may mean potential reversal of disease activity with IL-1β inhibitor therapy.

References

1 Muckle TJ, Wells SM. Urticaria, deafness and amyloidosis: a new heredo-familial syndrome. *QJM* 1962;**31**:235–48
2 Kummerle-Deschner J, Tyrrell P, Reess F, Kotter I, Lohse P, Girschick H *et al*. Risk factors for severe Muckle-Wells syndrome. *Arthritis Rheum* 2010;**62**:3783–91
3 Biswas D, Stafford N. Otolaryngological manifestations of "Muckle-Wells syndrome". *Int J Pediatr Otorhinolaryngol* 2010;**74**:553–5
4 Cuisset L, Drenth JP, Berthelot JM, Meyrier A, Vaudour G, Watts RA *et al*. Genetic linkage of the Muckle-Wells syndrome to chromosome 1q44. *Am J Hum Genet* 1999;**65**:1054–9
5 Kastbom A, Verma D, Eriksson P, Skogh T, Wingren G, Soderkvist P. Genetic variation in proteins of the cryopyrin

https://doi.org/10.1017/S0022215113001047 Published online by Cambridge University Press

inflammasome influences susceptibility and severity of rheumatoid arthritis (the Swedish TIRA project). *Rheumatology (Oxford)* 2008;**47**:415–17
6 Hawkins PN, Lachmann HJ, Aganna E, McDermott MF. Spectrum of clinical features in Muckle-Wells syndrome and response to anakinra. *Arthritis Rheum* 2004;**50**: trun 607–12
7 Aksentijevich ID, Putnam C, Remmers EF, Mueller JL, Le J, Kolodner RJ *et al*. The clinical continuum of cryopyrinopathies: novel CIAS1 mutations in North American patients and a new cryopyrin model. *Arthritis Rheum* 2007;**56**:1273–85
8 Hawkins PN, Lachmann HJ, McDermott MF. Interleukin-1-receptor antagonist in the Muckle-Wells syndrome. *N Engl J Med* 2003;**348**:2583–4
9 Rynne M, Maclean C, Bybee A, McDermott MF, Emery P. Hearing improvement in a patient with variant Muckle-Wells syndrome in response to interleukin 1 receptor antagonism. *Ann Rheum Dis* 2006;**65**:533–4

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Miss A C Leong takes responsibility for the integrity of the content of the paper
Competing interests: None declared