CONCISE REPORT

Hearing improvement in a patient with variant Muckle-Wells syndrome in response to interleukin 1 receptor antagonism

M Rynne, C Maclean, A Bybee, M F McDermott, P Emery

Ann Rheum Dis 2006;**65**:533–534. doi: 10.1136/ard.2005.038091

Background: Muckle-Wells syndrome (MWS), familial cold autoinflammatory syndrome, and neonatal onset multisystem inflammatory disease, also called chronic, infantile, neurological, cutaneous, and articular syndrome, are three hereditary autoinflammatory syndromes caused by mutations affecting the *CIAS1/NALP3* gene on chromosome 1q44. The proinflammatory cytokine, interleukin 1 β , is believed to have a fundamental role in their pathogenesis.

Case report: The case is described of a 59 year old white woman who presented with increasingly severe MWS-type features over a 15 year period. The response to interleukin 1 β inhibition with anakinra was dramatic, including a reduction in intracranial pressure with associated auditory improvement, as demonstrated by serial audiometry.

Conclusions: The confirmed improvement in hearing after initiation of interleukin 1 receptor antagonism corroborates previous reports that specific blockade of this single cytokine reverses most of the symptoms of this group of *CIAS1/NALP3* related autoinflammatory conditions, including the sensorineural deafness, which has not been previously reported.

Interleukin 1 β (IL1 β) has been implicated in the pathogenesis of a number of the hereditary periodic fever/autoinflammatory syndromes. One such disease, Muckle-Wells syndrome (MWS), is characterised by urticaria, progressive sensorineural deafness, and systemic AA amyloidosis. Other features include rigors, conjunctivitis, leucocytosis, raised acute phase reactants, and serum amyloid A levels. MWS is caused by mutations of the *CIAS1/NALP3* gene on chromosome 1q44, as are two other autoinflammatory conditions—familial cold autoinflammatory syndrome (FCAS) and neonatal onset multisystem inflammatory disease (NOMID), also called chronic, infantile, neurological, cutaneous, and articular (CINCA) syndrome. Rather than being classified as three distinct diseases, MWS, FCAS, and NOMID are now considered to represent a continuous spectrum of subphenotypes.

A number of recent case reports have documented the resolution of inflammatory symptoms and normalisation of serological values upon starting treatment with the IL1 receptor antagonist, anakinra.^{1–3} In a late presenting case of a variant of MWS, we describe confirmed reductions in intracranial pressure and cerebrospinal fluid (CSF) white cell counts, with auditory improvement upon competitive IL1 β inhibition with anakinra.

CASE REPORT

A 59 year old white woman presented with increasingly severe and intractable disease over a 15 year period. In

addition to displaying all of the aforementioned features of MWS, she also exhibited overlapping features with FCAS and NOMID/CINCA syndrome, as shown by exacerbation of her symptoms upon exposure to cold, papilloedema, chronic aseptic meningitis, and headaches caused by increased intracranial pressure.⁴ No other family members were affected. Upon starting treatment with anakinra, her inflammatory symptoms resolved completely within 24–48 hours, and rapid normalisation of her C reactive protein (from >160 mg/l to <10 mg/l) and serum amyloid A levels (from 415.0 mg/l to 12.6 mg/l) after 4 weeks.

In addition, her intracranial pressure and CSF white cell counts returned to normal. Before treatment with anakinra her highest opening pressure had been recorded at 42 cm CSF, with a maximum CSF white cell count of 35×10^6 /l. After 6 weeks of treatment her opening pressure had reduced to 19.5 cm CSF and her median CSF white cell count was 11×10^6 /l. These signs coincided with a dramatic reduction in the severity and frequency of her headaches.

Most notably, her hearing improved to the extent that she no longer requires the use of a hearing aid. Serial audiometry confirmed a 15–30 dB improvement in the 250–4000 Hz frequency range in each ear (fig 1). Her current pattern of hearing loss is more characteristic of degenerative sensorineural hearing loss (presbycusis), which one might expect to find in this age group.

No mutations of *CIAS1/NALP3* were demonstrated on DNA sequencing.

DISCUSSION

About 50 heterozygous missense mutations have been reported to date affecting the *CIAS1/NALP3* gene; however, these mutations have thus far been reported in only 60% of patients with MWS analysed.^{5–7} Although we found no *CIAS1/NALP3* mutation in this case, the overlapping features support the assertion that MWS, FCAS, and NOMID/CINCA syndrome represent a continuous spectrum of subphenotypes rather than three distinct diseases.^{8–11} MWS is dominantly inherited, but Aganna *et al*¹⁰ have reported at least one mutation (V200M, also designated V198M), also found in apparently healthy people, which may exhibit reduced penetrance in patients with FCAS/MWS. They further reported that symptoms in several female family members with another mutation (R262W, also designated R260W) substantially decreased with advancing age—in contrast with the natural history of our patient's condition.

Abbreviations: CINCA, chronic, infantile, neurological, cutaneous, and articular (syndrome); CSF, cerebrospinal fluid; FCAS, familial cold autoinflammatory syndrome; IL, interleukin; MWS, Muckle-Wells syndrome; NOMID, neonatal onset multisystem inflammatory disease

Figure 1 Hearing improvement in response to IL1 antagonism. Serial audiograms from the patient's left ear demonstrating a 15–30 dB improvement in the 250–4000 Hz frequency range within the first 18 weeks of treatment. Only results for the more severely affected left ear have been displayed for simplicity.

The confirmed improvement in hearing, intracranial pressure, and CSF white cell counts seen here with IL1 receptor antagonism further supports the targeting of this proinflammatory cytokine in the treatment of these auto-inflammatory conditions. The pathogenesis of sensorineural deafness in MWS is unclear, although it is postulated that expression of mutated *CIAS1/NALP3* in cartilage may have a role in the pathogenesis.¹¹

ACKNOWLEDGEMENTS

We are particularly grateful to the patient who agreed to participate in the study, as well as the referring physician.

Authors' affiliations

M Rynne, C Maclean, M F McDermott, P Emery, Academic Unit of Musculoskeletal Disease, Department of Rheumatology, Leeds General Infirmary, Great George Street, Leeds LS1 3EX, UK

A Bybee, National Amyloidosis Centre, 3rd Floor Lower, Royal Free and University College Medical School–Hampstead Campus, Rowland Hill Street, London NW3 2PF, UK

Correspondence to: Professor P Emery, P.Emery@leeds.ac.uk

Accepted 31 July 2005

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