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Menière-Like Syndrome in Camurati-Engelmann Disease

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Camurati-Engelmann disease is a rare autosomal dominant disorder characterized by cranial hyperostosis and sclerosis of the diaphyses of the long bones. To date only several hundreds of patients with Camurati-Engelmann disease have been reported. Among them, hearing loss was one of the most frequent cranial nerve manifestations (19%), followed by vertigo, facial nerve involvement, and trigeminal neuropathy [1]. While most of the reported cases with sensorineural hearing loss had a slowly progressive course, as would be expected in compression, fluctuating hearing loss with attacks of vertigo, resembling Menière disease, is extremely rare [2,3].

PATIENT DESCRIPTION

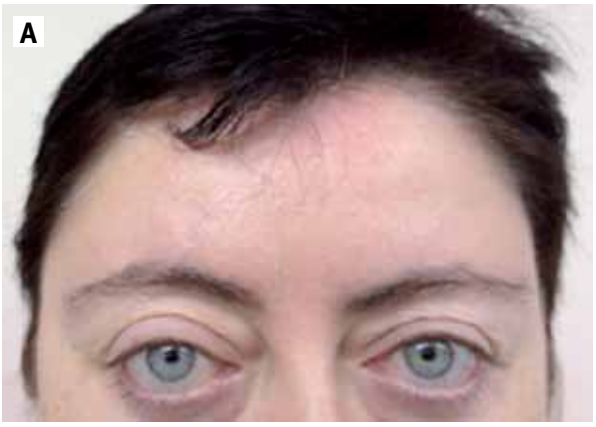
This 42 year old woman had a history of delayed motor development, chronic muscle fatigue and gait disturbance. Her mother and mother's brother suffered from similar symptoms. At the age of 20 she was diagnosed with Camurati-Engelmann syndrome. At that time she started to suffer from fluctuating tinnitus in the right ear and attacks of rotational vertigo lasting hours. The vertigo was accompanied by vomiting, increased tinnitus and blocked right ear.

On examination a bilateral exophthalmus and frontal bossing were conspicuous [Figure A]. On protrusion the tongue deviated to the left and a mild left muscle bulk atrophy was noted [Figure B]. The head thrust test demonstrated an abnormal vestibuloocular reflex with saccadic catch-up on both sides. Her gait was waddling but muscle dystrophy or long tract signs were absent. Repeated audiograms documented a sensorineural hearing loss at low frequencies during the period of disease activity that improved during remission. An electronystagmogram revealed a right caloric weakness. A computed tomography scan of the base of skull showed diffuse hyperostosis and sclerotization of the skull and face bones with stenosis of the internal auditory canals [Figure C]. Treatment with betahistine and low salt diet ameliorated the frequency of vertigo attacks.

COMMENT

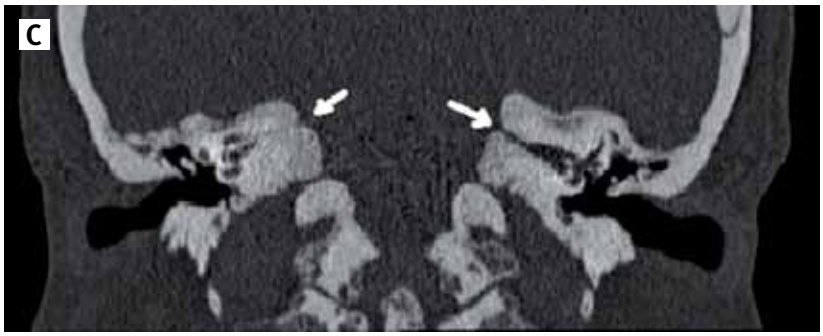
The genetic defect responsible for Camurati-Engelmann disease has been localized to the area of chromosome 19q13.2 coding for the tumor growth factor transforming growth factor-beta 1. Mutation in this gene leads to increased activation of osteoblasts and decrease of bone resorption [1]. Bone overgrowth of the skull causes stenosis of the foramina of the cranial nerves and their progressive compression.

The hearing loss in Camurati-Engelmann disease can be conductive, sensorineural or mixed [1]. The mechanism in Menière-like syndrome is not clear but may be attributed to the stenosis of the vestibular aqueduct, similar to the find-



[A] Bilateral exophthalmus and frontal bossing

[B] Left tongue atrophy



[C] CT scan of the skull base demonstrates narrowing of the internal auditory canals (arrows)

ing of a small diameter of bony vestibular aqueducts in Menière ears, predisposing to impaired endolymph drainage [4]. Another proposed mechanism is neurocompression at the narrowed internal acoustic canal, resulting in local demyelination and erratic axonal excitation [1]. In view of the good clinical response to betahistine and low salt diet, the presumed mechanism in this patient is probably endolymphatic hydrops, since symptoms of neurocompression are usually relieved by anticonvulsants.

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Capsule

Nonsense mutation in the *LGR4* gene is associated with several human diseases and other traits

Low bone mineral density (BMD) is used as a parameter of osteoporosis. Genome-wide association studies of BMD have hitherto focused on BMD as a quantitative trait, yielding common variants of small effects that contribute to the population diversity in BMD. Styrkarsdottir and team used BMD as a dichotomous trait, searching for variants that may have a direct effect on the risk of pathologically low BMD rather than on the regulation of BMD in the healthy population. Through whole-genome sequencing of Icelandic individuals, the authors found a rare nonsense mutation within the leucine-rich repeat-containing G-protein-coupled receptor 4 (*LGR4*) gene (c.376C>T), which is strongly associated with low BMD and with osteoporotic fractures. This mutation leads to termination of *LGR4* at position 126 and fully disrupts its function. The c.376C>T mutation is also associated with electrolyte imbalance, late onset of menarche and reduced testosterone levels, as well as an increased risk of squamous cell carcinoma of the skin and biliary tract cancer. Interestingly, the phenotype of carriers of the c.376C>T mutation overlaps that of Lgr4 mutant mice.

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Eitan Israeli

Capsule

The TLR4 antagonist Eritoran protects mice from lethal influenza infection

There is a pressing need to develop alternatives to annual influenza vaccines and antiviral agents licensed for mitigating influenza infection. Previous studies reported that acute lung injury caused by chemical or microbial insults is secondary to the generation of host-derived, oxidized phospholipid that potently stimulates Toll-like receptor 4 (TLR4)-dependent inflammation. Subsequently, Shirey et al. found that Tlr4–/– mice are highly refractory to influenza-induced lethality, and proposed that therapeutic antagonism of TLR4 signaling would protect against influenza-induced acute lung injury. Now they report that therapeutic administration of Eritoran (also known as E5564) – a potent, well-tolerated, synthetic TLR4 antagonist – blocks influenza-induced lethality in mice, as well as lung pathology, clinical symptoms, cytokine and oxidized phospholipid expression, and decreases viral titers. CD14 and TLR2 are also required for Eritoran-mediated protection, and CD14 directly binds Eritoran and inhibits ligand binding to MD2. Thus, Eritoran blockade of TLR signaling represents a novel therapeutic approach for inflammation associated with influenza, and possibly other infections.

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