A 16-year-old Male with Recurrent Inflammation and Hearing Loss
Josephine L. Reece, MD; Jeffrey D. Lancaster, MD; and Linda S. Nield, MD

A 16-year-old white boy was hospitalized for evaluation of recurrent headache, urticarial rash, low-grade fever, conjunctivitis, joint pain, and sensorineural hearing loss. The hearing loss had been diagnosed in the past year. However, the other symptoms had recurred at various intervals and lasted various lengths of time on several occasions throughout the past decade or more. At an unknown time in the past, he was diagnosed with Vogt-Koyanagi-Harada Syndrome (VKH) at another institution and lost to follow-up.

His physical examination for this admission revealed abnormal skin and eye findings. He had bilateral conjunctivitis and an erythematosus rash (see Figure) consisting of multiple wheals of varying sizes located on his arms and back.

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During his 5-day hospital stay, the rash spread to his abdomen and legs, but on some days, the rash was barely perceptible. His

For diagnosis, see page 754.

Editor’s note: Each month, this department features a discussion of an unusual diagnosis in genetics, radiology, or dermatology. A description and images are presented, followed by the diagnosis and an explanation of how the diagnosis was determined. As always, your comments are welcome via e-mail at pedann@slackinc.com.
Muckle Wells Syndrome

**DISCUSSION**

The diagnosis of VKH was doubted because of the absence of uveitis. VKH is an autoimmune disease commonly found in the Asian and Hispanic population, and it is characterized by vitiligo, alopecia, palsy of the eighth cranial nerve, aseptic meningitis, and the hallmark finding of bilateral posterior uveitis.

Because of the patient’s symptomatology, the cryopyrin-associated periodic syndromes (CAPS) and, more specifically, Muckle-Wells Syndrome (MWS) were strongly considered as the underlying diagnosis. The patient’s recurrent symptoms and the discovery of the patient’s missense mutation with substitution of an amino acid on gene \textit{NLRP3} were consistent with a diagnosis of MWS. Consultation with a pediatric rheumatologist was obtained for optimal management of this rare condition.

MWS is an autoinflammatory disorder characterized by intermittent episodes of rash; fever; arthralgia; conjunctivitis; sensorineural hearing loss; and secondary amyloidosis.\(^1\) Symptoms can occur as early as infancy, and usually by early childhood; however, some cases have onset in adolescence.

The skin is the organ most often involved, and the accompanying rash is described as urticarial-like with wheals of varying sizes located predominantly on the trunk and extremities. The eyes and large joints are the second and third most frequently affected organs, respectively.\(^2\) Conjunctivitis is the typical ocular manifestation.

Symptoms flare in a recurrent and unpredictable manner that can last hours to days. Sensorineural hearing loss will usually develop by adolescence. Laboratory studies will reveal chronically elevated acute-phase reactants, such as CRP and serum amyloid A. One-quarter of patients with the presence of elevated amyloid A will experience reactive amyloidosis and renal failure later in life.\(^3\)

First described in 1962, MWS belongs to the family of CAPS that include familial cold auto-inflammatory syndrome (FCAS) and chronic infantile neurologic cutaneous articular (CINCA) syndrome.\(^4\) Although classified as distinct diseases, all of these entities represent a spectrum of clinical findings, ranging from milder (FCAS) to the most severe (CINCA).

FCAS is characterized by cold-induced, day-long episodes of rash, arthralgias, headaches, fevers, and, less frequently, conjunctivitis. CINCA, the most severe of the CAPS, begins in the neonatal period, with continuous symptoms of fever, migratory non-pruritic rash, arthropathy, chronic aseptic meningitis, increased intracranial pressure, cerebral atrophy, seizures, and mental retardation. Patients suffering with CINCA will typically have hearing loss and more severe eye involvement, including uveitis, optic disc edema, and optic nerve atrophy that can lead to vision loss.\(^5\)

CAPS are inherited in an autosomal dominant fashion and are associated with a mutation (missense nucleotide substitution) on the \textit{CIASI} gene. Studies have revealed the overlap in mutations between FCAS and MWS and MWS and CINCA, which supports the claim that these disorders are just different phenotypic expressions of the same disease.\(^1,5,6,7\)

The \textit{CIASI} gene is named for cold-induced autoinflammatory syndrome \(^8\) and is expressed in peripheral leukocytes and chondrocytes. It encodes for the protein cryopyrin, which is responsible for inducing pro-interleukin-1 to its active form of interleukin-1 (IL-1).\(^6\) Interleukin secretion is usually regulated by the inflamasome, an intracellular protein complex that consists of cryopyrin, caspase-1, apoptosis-associated speck-like protein, and other proteins.

It is believed that mutations affecting cryopyrin production and, therefore, the regulation of the inflamasome, lead to the over-secretion of IL-1. This excess of interleukin leads to inflammation in multiple systems, thus produc-
ing the classic clinical symptoms of these disorders.3 Only a few hundred cases of CAPS have been identified in the US, indicating that MWS specifically is even rarer.3 Risk factors leading to the missense mutations have not been determined. Because of the rarity of these disorders, and perhaps clinicians’ lack of familiarity, CAPS often go misdiagnosed, contributing to the low number of known cases.

The diagnosis of MWS has always been based on clinical criteria, including the intermittent flare-ups without a known trigger. Sensorineural hearing loss, but not amyloidosis, is often present by the time diagnosis is made. In contrast, hearing loss does not occur with FCAS, and CINCA is more likely associated with central nervous system involvement and severe arthropathy.9

Although heterozygote mutations in CIAS1 gene have been found to be associated with MWS, FCAS, and CINCA, these diagnoses are still initially made on a clinical basis. Confirmation can be made by the presence of a missense mutation on CIAS1 gene. Although some mutations have so far exclusively been linked to one phenotype, several mutations are associated with different phenotypes.1

Initially, treatment for MWS is aimed at symptom management, specifically combatting the inflammatory process. Nonsteroidal anti-inflammatory drugs, colchicine, corticosteroids, and antihistamines have been used with little success, especially in preventing the recurrent attacks of MWS. Dapsone, azathioprine, mycophenolate mofetil, and infliximab have also provided limited relief. Subcutaneous anakinra, a recombinant non-glycosylated homolog of human IL-1Ra that inhibits binding of IL-1 to IL-1 receptor type 1 on target cells, has been studied in small, open-label trials.1

Rapid improvement in symptoms within hours to a few days with resolution of rash, fevers, arthralgias, conjunctivitis, and no recurrence of symptoms has been reported.1,7,8,10,11 Reduction in serum acute phase reactants, (most notably CRP), with resultant normal values in the first weeks of treatment has also been demonstrated. Yamazaki and Dalgic reported patient recovery from sensory hearing loss within months of treatment.9,10 In all studies, anakinra was well tolerated, with the most common adverse effect being a local reaction at the subcutaneous injection site. Although anakinra efficacy has been established in several small studies, the use of the medication is still considered off-label.

Rilonocept (or “IL-1 trap”), a human dimeric fusion protein that uses the extracellular domains of the IL-1 receptor, has also been studied in the management of CAPS. This drug blocks IL-1 activity by acting as a decoy receptor that binds IL-1 inhibiting it from binding to the cell surface receptors. A randomized, double-blind, placebo-controlled trial showed significant reduction and resolution of signs and symptoms of CAPS at a dose of 160 mg/week subcutaneously.3 Similar to anakinra, withdrawal of the drug resulted in recurrence of disease. Rilonocept has since been FDA-approved for treatment of MWS and FCAS patients aged 12 years and older.11

Another FDA-approved treatment for MWS and FCAS in those aged 4 years and older is canakinumab. Canakinumab is a fully humanized monoclonal antibody that specifically targets IL-1 beta.12

CONCLUSION

MWS should be considered as a diagnosis in a patient with recurrent, unexplained multisystem inflammatory episodes. Consultation with a pediatric rheumatologist for definitive diagnosis and treatment is essential to maximize the care in the child with this rare entity. Because of the increased risk of reactive amyloidosis, renal function will need to be monitored for life.

REFERENCES


