

Muckle–Wells syndrome

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Abstract

Muckle-Wells syndrome (MWS) is rare disorder characterized by chronic recurrent urticaria, periodic arthritis, sensorineural deafness, general signs of inflammation and secondary amyloidosis (AA type). The first symptoms of MWS are moderate fever and non-pruriginous urticaria that may become invalidating because they are almost permanent and begin during childhood. Other main inflammatory signs are located in the joints (arthralgia or arthritis) and eyes (conjunctivitis). Neurosensory hearing loss occurs during adolescence. The disease may be severe if generalized amyloidosis of the AA type occurs. Diagnosis is based on clinical signs, however genetic diagnosis is currently feasible. Hearing aids can improve deafness; recently, a treatment with the recombinant human IL-1 receptor antagonist anakinra showed a dramatic effect against inflammatory features of MWS. MWS is transmitted as an autosomal dominant disorder with variable expression within a family and from one family to another. The gene responsible for MWS was localized to chromosome 1q44 and identified. The CIAS1 (cold-induced autoinflammatory syndrome 1) gene is expressed in peripheral blood leukocytes and encodes a protein "cryopyrin" with the same N terminal domain than pyrin, protein associated to Familial Mediterranean Fever. Mutations in the NALP3/CIAS1/PYPAF1 gene are responsible for two other syndromes : familial cold autoinflammatory syndrome (FCAS) and CINCA (Chronic Infantile Neurological Cutaneous and Articular) syndrome.

Keywords

chronic urticaria, arthritis, deafness, amyloidosis, NALP3/CIAS1/PYPAF1 gene, 1q44 locus, cryopyrine, anakinra

Name of the disease and its synonyms

Muckle–Wells syndrome

Urticaria–deafness amyloidosis

Excluded diseases

Familial urticaria

Familial deafness

Hereditary amyloidosis type AA

Diagnostic criteria

They are purely clinical, however genetic diagnosis is currently feasible.

Differential diagnosis

This is a large group of diseases, many of which be considered as a function of the predominant clinical symptoms, which vary from one family to another, but also from one patient to another within the same family.

Incidence

It is unknown.

Clinical description

The first manifestations of Muckle–Wells syndrome consist of non-pruritic urticaria, starting during infancy, and sometimes debilitating because they are almost permanent, accompanied by a low-grade fever. The other inflammatory signs are mainly joint (arthralgias or arthritides) and/or ocular (conjunctivitis) involvement.

These inflammatory signs are associated with neurosensory deafness that starts during adolescence. The severity of the disease resides in the inconstant occurrence of generalized amyloidosis type AA.

The autosomal dominant inheritance has variable intra- and interfamilial expression.

Management including treatments

Hearing aids can correct deafness to some extent. Recently, a treatment with the recombinant human IL-1 receptor antagonist Anakinra showed a dramatic effect against inflammatory features of MWS.

Etiology

The gene responsible for Muckle–Wells syndrome was localized to chromosome 1q44 in 1999 and recently identified. The *CIAS1* (cold-induced autoinflammatory syndrome 1) gene is expressed in peripheral blood leukocytes and encodes a protein "cryopyrin" which the same N terminal domain than pyrin, protein associated to [Familial Mediterranean Fever](#). Mutations in the *NALP3/CIAS1/PYPAF1* gene are responsible for two other syndromes: familial cold autoinflammatory syndrome (FCAS) and [CINCA](#) (Chronic Infantile Neurological Cutaneous and Articular) syndrome.

Biological methods of diagnosis

No biological sign specific to Muckle–Wells syndrome has been identified; only moderate non-specific signs of inflammation during the course of inflammatory attacks are known. Some

biochemical analyses are useful to exclude certain diseases that can be considered as a function of the clinical signs present.

Unresolved questions and comments

The existence of other clinical signs in some families suggests the possibility of genetic heterogeneity.

The remarkable response of MWS to anakinra suggests that IL-1beta has a fundamental role in the pathogenesis of inflammation associated with mutations in the *NALP3/CIAS1* gene, and supports study of IL-1 inhibition in patients with NOMID/CINCA syndrome or FCAS. The clinical features of the various syndromes associated with mutations in the *NALP3* gene may overlap to a greater extent than has previously been recognized.

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