CLINICAL CASE OF PATIENT WITH CRYOPYRIN-ASSOCIATED PERIODIC SYNDROME (MUCKLE-WELLS SYNDROME) AND SYSTEMIC LUPUS ERHYTHEMATODES

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Abstract. *Muckle-Wells syndrome is a cryopyrin-associated periodic syndrome with an autosomal dominant transmission pattern. The disease characterized by episodes of step move. We present a clinical case a woman of 34-years old with cryopyrin-associated periodic syndrome (Muckle-Wells syndrome) and systemic lupus erhythematodes (SLE). Patient is a heterozygous carrier of a 3-nucleotide duplication in exon 3 of the NLRP3 gene (c.1315_1317dupGCG), inserting an alanine between amino acid positions 439 and 440 (p.Ala439dup). This mutation is a characteristic with Muckle-Wells syndrome. From the clinical examination she has clinical symptoms of SLE with moderate activity from SLEDAI = 9 points ("malar rash", arthritis, leucopenia with lymphopenia, elevated levels of ANA-antibodys and anti-dsDNA-antibodys). Patient was treatment with methylprednisolone 12 mg daily, methotrexate 15 mg weekly, colchicin 2 time of 0,5 mg daily. Over 3 months patient has partial improvement of symptoms without full reduction. On the moment patient lives in Germany and has treatment with Anakinra with excellent results and good quality of life. In the literature is not found other with connection between cryopyrin-associated periodic syndrome (Muckle-Wells syndrome) and connective tissue disease.*

Key words: *Muckle-Wells syndrome, systemic lupus erhythematodes*

Introduction

Muckle-Wells syndrome is a cryopyrin-associated periodic syndrome with an autosomal dominant transmission pattern. The disease characterized with episodes of of fever, arthritis, urticarial rash, arthralgia and abdominal pain. Subsequently, the patient may be found to have progressive sensorineural deafness and multiorgan AA amyloidosis. It is caused by the mutation of the NLRP3 gene (CIAS1), which encodes cryopyrin. It is protein responsible for the regulation of the production of inflammatory cytokines, mainly interleukin (IL)-1β, which leads to a persistent and uncontrollable systemic inflammation and autoinflammatory diseases cryopyrin-associated periodic syndromes (CAPS) [1, 2, 3].

We present a clinical case a woman of 34-years old with cryopyrin-associated periodic syndrome (Muckle-Wells syndrome) and systemic lupus erhythematodes (SLE). The first clinical symptoms of the disease started on 3-months old, observed by mother and paediatrician.

Clinical symptoms characterized with episodes of:

✓ fever up to 38.5 degrees Celsius

✓ arthritis of metacarpophalangeal and metatarsophalangeal joints, ankles, knees, resolve within 1-2 days

✓ erythema rash on the body and limbs

✓ asthenoadynamic syndrome

✓ conjunctivitis and sensorineural deafness

Patient has many hospitalisations in the clinic of dermatology and rheumatology. Differential diagnoses include inflammatory joint disease and connective tissue disease. There are no defined diagnostic criteria for confirming diagnosis. The episodes of flair are repeat in the years. Treatment is initially based on methylprednisolone, colchicin, metamizol, nonsteroidal anti-inflammatory drugs (NSAID). Most attacks resolve within 12 hours and repeat every 3 days. On the 32 years old is performed genetic analysis. Patient is a heterozygous carrier of a 3-nucleotide duplication in exon 3 of the NLRP3 gene (c.1315_1317dupGCG), inserting an alanine between amino acid positions 439 and 440 (p.Ala439dup). This mutation is a characteristic with cryopyrin-associated periodic syndromes (CAPS) type Muckle-wells syndrome. Genetic analysis is performed in Institute of laboratory medicine and human genetics, Singen, Germany.

On the 45-year-old woman is hospitalise in the clinic of rheumatology.

Clinical symptoms characterized with episodes of:

✓ fever up to 40 degrees Celsius

✓ asthenoadynamic syndrome

✓ arthritis
✓ diffuse oedema of the fingers.
✓ At the same time is established
✓ sensorineural deafness (neuritis acoustic right and left)
✓ “malar rash”
✓ Raynaud disease
✓ Myalgia’s and malaise in proximal muscles on the limbs (Fig. 1).



Fig. 1. Episodes of rash and urticaria in patient Muckle-Wells

Laboratory tests showed increase ESR 40 mm (normal < 15 mm); C-reactive protein 30 g/l (normal < 5 g/l); anaemia with low serum iron, leucopenia with lymphopenia, proteinuria 0.32 g/l (< 0.15 g/l) Immunological tests revealed elevated levels of ANA-antibody’s 1:1280 (normal < 1:80), three time examination of elevated levels of anti-dsDNA 68,9; 62,4; 34 U/l (норма < 25 U/l) whining negative other ribonucleoproteins. Laboratory tests showed increase ACL IgM, IgG, β2GPI antibody’s, annexin antibody’s.

Skin-muscular biopsy it`s done. Result from evaluation of the skin present perivascular inflammation, proliferation of the endothelial cells in the vesell’s, acanthosis. Result from evaluation of the muscle present: mononuclear cells infiltration in the muscular cells, atrophy of the rhabdomyocytes, degenerative changes. Histological examination present nonspecific dermatitis. This result is associated with myositis. Lupus band test it’s done and results is positive.

Differential diagnoses include:

✓ Autoinflammatory diseases cryopyrin-associated periodic syndromes + SLE with moderate activity from SLEDAI = 9 points (“malar rash”, arthritis, leucopenia with lymphopenia, elevated levels of ANA-antibodys and anti-dsDNA-antibodys).

✓ Autoinflammatory diseases cryopyrin-associated periodic syndromes + SLE with moderate activity from SLEDAI = 9 points (“malar rash”, arthritis, leucopenia with lymphopenia, elevated levels of ANA-antibodys and anti-dsDNA-antibodys) + myositis (muscle weakness and histological change in the biopsy)

Patient was treatment with methylprednisolone 12 mg daily, methotrexate 15 mg weekly, colchicin 2 time of 0,5 mg daily. Over 3 months patient has partial improvement of symptoms without full reduction. On the moment patient lives in Germany and has treatment with Anakinra with excellent results and good quality of life.

Discussion

Cryopyrin activate capsase-1 and NF-kappa β leads to inflammatory cytokines and associated with autoinflammatory response (Fig. 2).

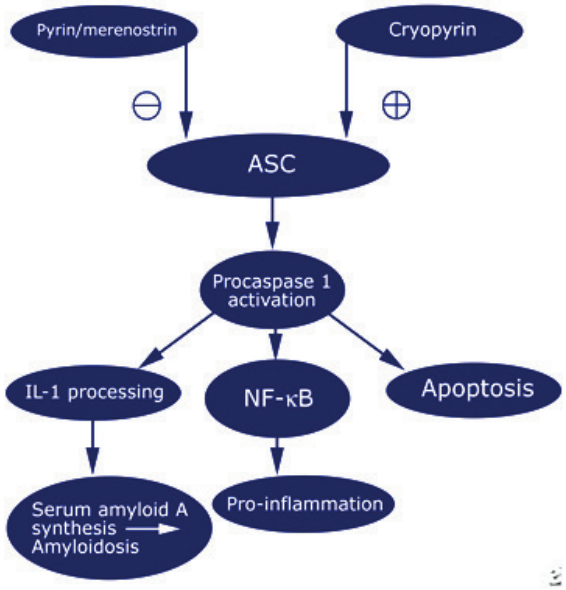


Fig. 2. Pathogenesis of Cryopyrin-associated Periodic Syndrome

Muckle-Wells syndrome is a rare hereditary disease with an autosomal dominant transmission pattern. It is caused by the mutation of the NLRP3 gene (also referred to as CIAS1), which encodes cryopyrin, a protein responsible for the regulation of the production of inflammatory cytokines, mainly interleukin (IL)-1β, which leads to a persistent and uncontrollable systemic inflammation. There are 3 types of cryopyrin-associated periodic syndromes (CAPS) of increasing severity: familial cold autoinflammatory syndrome, Muckle-Wells syndrome and chronic infantile neurologic, cutaneous, articular (CINCA) syndrome and neonatal onset multisystem inflammatory disease (NOMID) [3, 4] (Fig. 3).

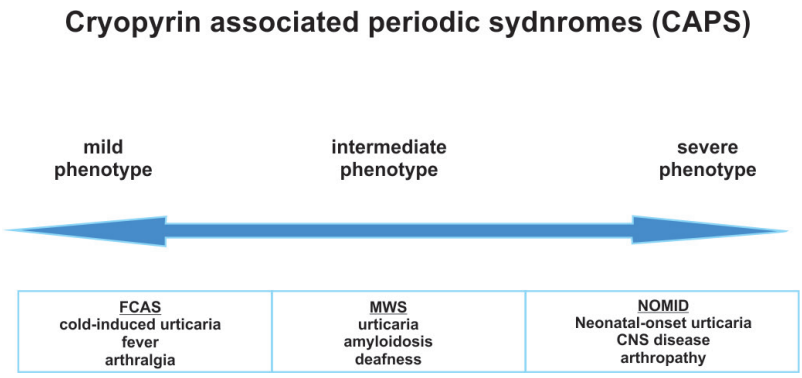


Fig. 3. Cryopyrin-associated Periodic Syndrome

Muckle-Well Syndrome is characterized by:

- Triad – urticarial rash, sensorineural hearing loss, amyloidosis
- Debut – often in adolescence
- Most attacks continue within 24-28 hours
- Intermittent episodes of fever
- Urticarial rash on the body and limbs
- Arthralgia, myalgia
- Generalised lymphadenopathy
- Sometimes with pleuritis
- During the attacks, levels of C-reactive protein may be increased
- Amyloidosis [1, 5].

Kineret (Anakinra) by Biovitrum pharmaceuticals, an IL-1 receptor antagonist, has been used extensively in MWS patients with excellent clinical results. However, it is not currently approved by the FDA for the treatment of MWS or any of the CAPS diseases [6, 7, 8].

Arcalyst (Rilonacept) by Regeneron Pharmaceuticals, an interleukin-1 blocker, was approved by the FDA in 2008 for the treatment of CAPS, including FCAS and MWS, in adults and children 12 and older [6, 7].

Ilaris (Canakinumab) by Novartis Pharmaceuticals, a monoclonal antibody to interleukin-1 beta, was approved by the FDA in 2009 as a treatment for children and adults with CAPS, including FCAS and MWS [6, 7].

Hereditary recurrent febrile syndromes are a group of monogenic diseases and the first to be characterized as autoinflammatory. They are associated with disorders of innate immunity. Muckle-Wells Syndrome is a monogenic disease. SLE is polygenic autoimmune disease. On the basic of the autoinflamatory syndromes standing disfunction of the innate immunity and mutation of the genes and they products participate in detection on gangerous sygnales and control of inflammation by the cytokines. Unlike autoimmune disorders such as systemic lupus erythematosus, in which the disease is caused by abnormalities of the adaptive immune system, people with autoinflammatory diseases do not produce autoantibodies or antigen-specific T or B cells. Instead, the autoinflammatory diseases are characterized by errors in the innate immune system. To our knowledge, there have been only 21 published cases, including our case, on the coexistence of Familial Mediterranean fever (FMF) and SLE, but no Muckle-Wells Syndrome and SLE [9]. In rheumatoid arthritis and SLE is activated overlap mechanism on innate immunity. It is possible to stimulate innate immunity and to determine proinflammatory character of the disease. So systemic disease is activate innate immunity. This is explicate what many clinical symptoms in SLE exist in autoinflammatory diseases.

Differential diagnoses include other periodic inflammatory disorders such as tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS), hyperimmunoglobulinemia D with periodic fever syndrome (HIDS), juvenile systemic granulomatosis, juvenile idiopathic arthritis, familial Mediterranean fever (FMF), Behçet disease, Still disease. Other autoimmune diseases could also be evoked as hypocomplementemic vasculitis or systemic lupus.

Conclusion

In the literature have been published cases with MWS, but no combination of Muckle-Wells Syndrome and systemic disease. Importantly, the NALP3 inflammasome is involved in the pathogenesis of other inflammatory disorders. Understanding the pathophysiology of rare conditions can, therefore, identify potential new therapeutic options for treatment of patients with these relatively common diseases.

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