

PROJ MEETING REPORT

Highlights of the III. International Conference on Familial Mediterranean Fever and Hereditary Inflammatory Disorders

The 3rd International Conference on Familial Mediterranean Fever (FMF) and Hereditary Inflammatory Disorders was held in La Grande Motte, France during 23-27 Sept. 2002. A total of 175 abstracts were presented along with lectures on FMF and non-FMF hereditary inflammatory disorders. The non-FMF inflammatory disorders included hyper immunoglobulinemia D syndrome (HIDS), TNF-receptor associated periodic fever syndrome (TRAPS), familial cold urticaria (FCU) or familial cold autoinflammatory syndrome (FCUS), Muckle Wells Syndrome (MWS) and chronic infantile neurological cutaneous arthropathy (CINCA) or neonatal onset multisystem inflammatory disease (NOMID) syndrome. This report summarizes the presentations at this meeting.

Introduction:

The most common periodic fever disease or autoinflammatory disorder is FMF(1). FMF and HIDS have an autosomal recessive inheritance. HIDS is caused by mutations in the gene encoding for mevalonate kinase (MVK) (2,3). TRAPS, MWS and FCU are autoinflammatory disorders with an autosomal dominant inheritance. TRAPS is caused by missense mutations in the extracellular domain of the 55Kda TNF receptor (TNFRSF1A) (4). Sporadic cases have been reported to occur in some 2%.

The MWS/FCU is caused by mutations in the NACHT domain of the "cold induced auto inflammatory syndrome" (CIAS) gene on 1q44 (5). Interestingly MWS and FCU may be associated with the same mutation. Furthermore CINCA has also been mapped to the same gene, with different mutations so far (6). However, clinical overlap may be expected with these disorders. There have been a considerable number of patients with typical phenotypes of these diseases, but no mutation in the CIAS gene suggesting genetic heterogeneity. Similarly there are many patients who have an FMF phenotype and who do not have any

MEFV mutations. A good deal of patients with periodic fever do not display any mutation in any of the genes identified so far thus suggesting the presence of even more genes or maybe even more diseases in the group of periodic fever syndromes.

Dr Kastner has reminded us of another autoinflammatory disease, pyogenic arthritis with pyoderma gangrenosum and acne (PAPA) syndrome that is also associated with mutations in this group of proteins.

Pathogenesis:

We now understand that the pyrin/co-pyrin proteins are effective in the IL-1 pathway. Dr Gumucio has outlined the role of pyrin domain containing proteins in inflammation and apoptosis (7). Both pyrin and co-pyrin interact with a common adaptor protein, ASC ("apoptosis associated speck-like protein which contains a caspase recruitment domain), which stimulates caspase-1 activation. Subsequently this leads to IL-1 processing and secretion, along with NF κ B activation and apoptosis (7). IL-1 beta and NF κ B subsequently induce the proinflammatory response. Thus these processes play a very important role in the inflammatory pathways that characterize the innate immune system (7). NF κ B is subsequently involved in the resolution of the inflammatory response as well.

Dr Frenkel (8) has introduced evidence that in the MVK deficiency of HIDS, IL-1beta secretion is also increased and this is probably due to the lack of isoprenoids that are downstream elements in the MVK pathway. Thus all the aforementioned periodic fever syndromes seem to share a common pathway through IL-1. Knockout models from Dr Kastner's lab have shown that pyrin deficient mice show increased IL-1beta, although it has been emphasized that this experimental model was not perfect. Mouse and rat homologs of MEFV will help us study the function of pyrin (9).

Pyrin localizes in the microtubules with actin-cytoskeleton (10). Thus we need to complete the pieces of the puzzle. This localization has led a group of researchers to investigate if a mutation in pyrin rendered the person more capable of killing intracellular

microbes. My work has reminded us that the carrier rate is between 1/3-1/5 among the eastern Mediterranean populations (11). Thus it is conceivable that heterozygotes for the MEFV mutations might have had a survival advantage just as the sickle cell trait has against malaria. However, large populations need to be studied to reach conclusions and no substantial evidence has been reached so far (11).

Clinical Features:

Dr Pras (12) has shortened the diagnostic criteria for FMF into: 1. recurrent short inflammatory attacks + 2. Favorable response to colchicine treatment. In 50-70% of the patients with phenotype either we are able to find 1 mutation only or we do not succeed in demonstrating even 1 MEFV mutation.

Dr Drenth (13) has outlined the typical features of all periodic fever diseases. Typical attacks of FMF last for 1-3 days with fever and serositis. Most patients with HIDS are Dutch and attacks last 3-7 days. Fever may be accompanied by lymphadenopathy, arthralgia/arthritis, and skin disease. The serum IgD is greater than 100 IU/ml. The attacks of TRAPS are longer than 1 week and patients usually suffer from arthralgia, myalgia, abdominal pain, and skin rash as well as conjunctivitis and periorbital edema. The spectrum of symptoms in TRAPS is considerable. In FCAS attacks last <1 day and skin lesions occur after cold exposure. In MWS the attacks last for 1-2 days and arthralgia/arthritis and an urticarial rash often accompany the fever. Late onset deafness is common (13).

CINCA is defined by skin lesions, chronic aseptic meningitis, fever, lymphadenopathy and enlarged patellae along with dysmorphic features (6, 13).

Secondary amyloidosis may occur in all except HIDS. Common features of periodic fever syndromes are the raised acute phase reactants. Dr Hawkins (14) has presented data that the only known prerequisite for developing amyloidosis is sustained and substantial elevation of plasma SAA concentrations and has urged us to follow the levels in monitoring

disease activity. Elevated SAA may be an indication for treatment in asymptomatic children (14).

Treatment:

The established treatment for FMF is colchicine at an effective dose (1,12). In TRAPS inhibitors of TNF along with alternate day steroids seem to be effective. In HIDS a recent study with statins has shown promising results although it needs to be pursued in children (15). There is no reliably effective treatment in MWS and FCUS. NSAIDs and steroids have been tried with varying success (13). Steroids are indicated in CINCA as well.

Understanding the pathogenesis of the periodic fever symptoms will help us in understanding the inflammatory pathways in general. More research in this field is critical. In the meantime, as doctors taking care of children we need to be excellent, conscientious clinicians that diagnose our periodic fever patients before they suffer from unnecessary investigations and the complications of these diseases.

References:

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