14. *Clinical and histological improvement during 5 years of treatment of a woman with Muckle-Wells Syndrome*

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A "heredo-familial"syndrome was described by Muckle and Wells in 1962 (and given their names in 1979), including urticaria, deafness and amyloidosis. MWS is one of 3 overlapping periodic cryopyrinopathies, with incidence <1/400,000, and autosomal dominant inheritance. It involves dysregulation of the inflammasome, specifically of IL-1β. It presents from infancy, typically with fevers, urticaria, arthralgias and arthritis, later with sensorineural hearing loss, and AA amyloidosis in 25%, some with renal insufficiency. Its rarity can lead to delayed diagnosis. The advent of therapy with specific drugs that decrease the excessive IL-1β action revolutionized clinical outcomes, though with few data on that of established amyloidosis. The interdisciplinary care of our patient is described.

Our patient is a 43 year old woman of Greek, Icelandic and German descent. She had urticaria and periodic fevers from birth. Arthralgias occurred at age 7, then "migraine" headaches and "papilledema". She was diagnosed with "ill-defined connective tissue disease" as no single autoimmunity diagnosis fit. Symptoms worsened by age 13 years: multiple arthralgias were treated with ibuprofen. Prednisone for 6 months improved the arthralgia, hives and fatigue. Because of side effects it was replaced by hydroxychloroquine, without effect. At age 28, she was admitted with fatigue, anemia and thrombocytopenia, without etiologic diagnosis. A 6 month course of prednisone improved these and the rash. During pregnancies at ages 31 and 35, the chronic symptoms were complicated further by migratory arthritis. Both required early Caesarean deliveries.

Diarrhea and anorexia began at age 36, and worsened progressively, resulting in severe cachexia (weight loss of >15 kg), by age 38. In addition to previous symptoms, she had severe headaches, dry eyes, a goitre, neck lymphadenopathy, multiple subcortical hyperintense foci, subdural effusions and arachnoid adhesions on MRI, moderate hearing loss and 3g/d proteinuria. Amyloid was found in biopsies of stomach, duodenum and a lymph node, with mass spectrometric analysis of peptides showing an (S)AA profile. A heterozygous D30SN mutation of the NLRP3 gene was found, diagnostic of MWS.

Canakinumab, a selective anti-IL-1β monoclonal antibody, was started at 150 mg im, q8 wks. Total parenteral nutrition with marked reduction of PO intake to minimize the diarrhea were initiated, and continued nightly at home, with gradual restoration of nutritional status. Rapid and progressive improvement in many MWS symptoms and CRP occurred, but headaches and temperature sensitivities persisted. After 1 yr, therapy was changed to anakinra, a selective IL-1β receptor antagonist, as it has better CNS penetration. Doses were increased from 100 mg im daily to 300 mg over 1 yr, with relief of headaches and maintenance of all other improvements. With TPN and gradual improvement in GI absorption, TPN was reduced stepwise to 4 nights/wk, and weight increased from its lowest of 42 kg, to 55 kg at age 40 yrs, stabilizing at 58 kg. The proteinuria disappeared, and her hearing stopped worsening. Follow-up GI biopsies showed *no amyloid*. She works full time, and manages the burden of her son, now age 7, whose treatment for MWS has restored his health and development as well!

This case is presented to raise consciousness of MWS as one of the cryopyrinopathies. Early treatment can dramatically reverse many symptoms and prevent long-term consequences. In addition, in our case, despite a tardive diagnosis, treatment was unexpectedly able to reverse the GI (proven) and renal and CNS (presumed) complications due to (S)AA amyloidosis.