Yao syndrome in pregnancy

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Background

Yao syndrome, formerly *NOD2*- autoinflammatory disease and immunodeficiency (NAID), is a systemic autoinflammatory disease (SAIDs) associated with periodic fevers, arthritis, dermatitis, distal extremity swelling, serositis, gut symptoms and sicca-like syndrome [1][3]. It is genetically linked to specific *NOD2* sequence variants like Crohn disease and Blau syndrome [3][1]. Preliminary studies suggest that NAID may involve alterations in the cytokine IL-17, Th17 cells and specific regulatory T cells [4]. Yao syndrome is diagnosed if 2 major criteria, at least one minor criterion, the molecular criterion, and exclusion criteria are fulfilled as shown in Table 1 [4].

Table 1 The Diagnostic Criteria for Yao Syndrome

Clinical criteria	
Major	
1	≥ 2 periodic occurrences
2	Recurrent pyrexia or dermatitis or both
Minor	
1	Oligo- or polyarthralgia/inflammatory arthritis or distal extremity swelling
2	Abdominal pain, diarrhoea or both
3	Sicca-like symptoms
4	Pericarditis/pleuritis or both
Molecular criterion	NOD2 IVS8 +158 or R702W or both, or other rare variants
Exclusion criteria	High titre antinuclear antibodies, inflammatory bowel disease, Blau syndrome, adult sarcoidosis, primary Sjögren syndrome and monogenic autoinflammatory diseases

Case

A twenty-year old primigravida with a severe autoinflammatory syndrome requiring intensive immunosuppression fell pregnant on contraception, and was jointly managed by the Fetal Medicine Unit and the Immunology team of The Canberra Hospital. She was diagnosed with Yao Syndrome in 2014 when she initially presented with an unexplained systemic inflammatory response associated with fevers, myalgia, arthralgia, an evanescent palpable urticarial rash on her back and trunk and an unsteady gait.

Her blood panel revealed an elevated erythrocyte sedimentation rate (ESR) ranging between 50 -100mm/hr, C-reactive protein (CRP) of over 300mg/L, neutrophilia of 18.4x109/l and no anaemia. Her blood cultures and autoimmune serologies including ANCA, ANA, ENA, double-stranded DNA and HLA-B27 were negative while an abdominal CT scan, chest X-ray and a whole-body bone scan was unremarkable. The disease peaked with severe joint pains in the hips, knees and ankles, limiting weightbearing. Symptom control with anti-inflammatory agents was achieved while several working diagnoses were ruled out, including underlying infection and a suspected Mendelian autoinflammatory disease. Other than an unexplained history of joint disease of the wrists and feet in adolescence and reflux nephropathy up till the age of two, she was otherwise healthy and well.

A genome sequencing was subsequently initiated and a causal mutation in *NOD2* was identified, consistent with Yao syndrome. Following a trial of several regimens, she was stabilised on Tocilizumab (IL-6 receptor antagonist), Anakinra (interleukin (IL)-1b receptor antagonist), methotrexate and prednisolone. She received high dose prednisolone of 10mg in the first trimester and 100mg Aspirin daily. She had a normal morphology scan. Her symptoms recurred in the form of subcutaneous nodules in the extensor surface of her wrist and morning stiffness with a persistently raised CRP level at 120mg/dL. This time, she did not experience fevers or cutaneous manifestations and remained normotensive. With the emergence of gestational diabetes, optimising her steroid dose was challenging whereby a dose increase to 25mg daily contributed to hyperglycaemia. Given the ongoing inflammation risking the pregnancy, a decision was made to start her on a tumor necrosis factor inhibitor, hence she was commenced on Infliximab until 32 weeks of gestation. At 33 weeks, she ruptured her membranes prematurely and delivered a healthy baby weighing 2370g. She progressed well postpartum on infliximab and a tapering steroid regimen by 1g each month and slowly switched back to her previous treatment.

Discussion

There is limited information surrounding the occurrence and management of Yao syndrome in pregnancy. Of 52 patients of a non-pregnant population in a study that analysed treatment outcomes of this disease, 19 patients (36.6%) achieved marked reduction in duration and severity of disease flare with a short course of glucocorticoids of 30-40mg prednisolone, administered for 3-4 days, particularly in those with less frequent flares. In cases of higher recurrence, a prolonged course of corticosteroids may achieve similar results [3]. Another case report in the United States suggested successful symptom control within three months of 2g Sulfasalazine [SSZ] daily without corticosteroids. Here, the role of Sulfasalazine in inhibition of cytokine release like interleukin, TNF and NF – [kappa]B may directly suppress the disease [5]. A large cohort study inclusive of 54 patients with NAID, prednisolone and sulfasalazine showed most effective against arthritic symptoms, which was not achieved with NSAIDs. The same study described average results with biologics like infliximab and tocolizumab – two agents that were effective in our patient including in pregnancy. [2]

In conclusion oral corticosteroids and biologic agents are considerable empirical therapy of choice for Yao syndrome in pregnancy if further supported by stronger evidence for its use while the role of sulfasalazine can still be explored.

References

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