Case of Fatal Meningitis in an adult patient with IRAK4 Deficiency

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To the Editor

The female Caucasian patient, born to non-consanguineous parents, first presented at 1 week of age with mastitis treated with oral flucloxacillin. Within the first year of life, she re-presented on several occasions with severe infections requiring antibiotic treatment including *Haemophilus influenzae B* meningitis and *Pseudomonas* septicaemia complicated by respiratory arrest necessitating ventilation. She had received her childhood vaccinations as per the immunisation schedule but had no further vaccinations since the age of 2. Despite commencing prophylactic antibiotics and immunoglobulin replacement therapy, her clinical course continued to be characterised by a series of life-threatening infections including episodes of meningitis, septicaemia and osteomyelitis. Other infections included otitis media, pharyngitis and parotid and skin abscesses. Microbiological samples yielded a variety of bacteria including *Haemophilus influenzae, Pseudomonas, Streptococcus pneumoniae, Staphylococcus aureus and Streptococcus pyogenes.* Aged 13, a CD62L shedding assay showed a defective response to lipopolysaccharide and a normal response to phorbol myristate acetate (PMA), a TLR independent stimulator. Genetic analysis revealed a homozygous c.877C>T (p.Q293X) mutation in the IRAK-4 gene, confirming IRAK-4 deficiency.

In her late teenage years, her infection burden significantly decreased, prophylactic antibiotics were stopped, and she was managed on subcutaneous immunoglobulin therapy alone. The decision was made to decrease the dose gradually to discontinue and re-evaluate her functional antibody responses. Infection burden remained low on half the original dose of immunoglobulin replacement for more than 12 months. However, aged 25 she presented to her local Accident and Emergency department with an acute headache, vomiting and a fever of 39.8 degrees Celsius. She was haemodynamically stable, and GCS was 15/15. Following admission to hospital, she experienced a seizure, her temperature increased to 40 degrees Celsius, GCS deteriorated to 9/15 and she became haemodynamically unstable. She underwent tracheal intubation for mechanical ventilation and was transferred to the intensive care unit. She required inotropic support and treatment with Amoxicillin, Ceftriaxone and Aciclovir was commenced. A CT scan of the head demonstrated diffuse vasogenic oedema with significant mass effect, effacement of basal cisterns and brainstem herniation. White blood cell count and CRP were raised at 14 $x10^9$/L and 212 mg/L respectively. The patient was transferred to a tertiary neurocritical care unit for neurosurgical support and intervention. Prior to transfer, fixed and dilated pupils were noted on examination and a repeat CT head showed gross cerebral oedema with herniation of the brain stem. She sadly passed away within 24 hours of transfer with brain stem death. *Streptococcus pneumoniae* was isolated, (strain unknown), from a CSF sample obtained after insertion of an external ventricular drain.

IRAK-4 (interleukin-1 receptor-associated kinase 4) deficiency is an inherited autosomal recessive primary immunodeficiency leading to increased susceptibility to severe, pyogenic infections. These are often invasive in nature and present frequently as meningitis, septicemia, osteomyelitis and abscesses. Other reported infections include septic arthritis, pharyngitis, adenitis, otitis media and sinusitis. The range of bacterial infections is narrow, often caused by *Streptococcus pneumoniae*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*[1,2] with recurrent invasive pneumococcal disease predominating [1]. Viral, parasitic and fungal infections are uncommon. Delayed separation of the umbilical cord has been reported as a non-infectious feature. Systemic signs of inflammation may be weak or delayed with minimal or absent fever and limited increase in inflammatory markers.

IRAK-4, a serine threonine kinase, is essential in the innate TLR (toll like receptor) canonical pathway. TLRs respond to conserved microbial antigens collectively referred to as pathogen associated molecular patterns (PAMPs). Examples of these include lipopolysaccharides, flagellin, peptidoglycan and lipoteichoic acid. TLRs are largely classified into two subgroups

based on their localisation. Most TLRs, apart from TLR3 and TLRs 7-9, are present on the cell surface and bind extracellular PAMPs. Upon ligand binding, TLRs induce signal transduction via their cytoplasmic Toll/IL-1 receptor (TIR) domain. MyD88, a cytosolic adaptor, serves as a bridge between TIRs and the IRAK complex. Activation of this pathway results in NF-κB recruitment and the transcription of genes encoding inflammatory cytokines such as Il-1, IL-6, TNFa and interferons. Of the 10 known TLRs, only TLR3 does not utilise MyD88 and IRAK-4 for signalling. This was initially suggested as an explanation for why the type 1 interferon pathway is largely unaffected and the risk of viral infections is negligible in IRAK-4 deficiency[2], although subsequent reports have suggested otherwise[3].

IRAK-4 deficiency was first described in 2003 in 3 unrelated children with limited inflammatory responses and recurrent pyogenic infections secondary to *Streptococcus pneumoniae* and *Staphylococcus aureus*[4]. Although deaths have been reported in the IRAK-4 deficient cohort, these have not occurred beyond the teenage years. Immunological maturity with the acquisition of adaptive immunity and immunological memory may explain the significant decline in infection burden with time[5]. Early initiation of antibiotic prophylaxis and/or immunoglobulin replacement therapy and anti-pneumococcal vaccination have all been reported as beneficial treatment interventions[1]. One of the largest international studies analysed the records of 48 patients from 31 kindreds. 39% of patients had died of invasive bacterial infections before the age of 8, and mostly before the age of 2. 61% of these deaths were secondary to invasive pneumococcal disease. A high proportion had suffered their first bacterial infection early in life; 31.2% during the neonatal period, 54% before the age of six months and 87.5% before the age of 2 years. No invasive bacterial infections were seen beyond the age of 14, although one patient continued to experience occasional skin infections[1]. Most recently, a female patient in her 30's was described with recurrent pyogenic infections, predominantly pneumonia, with ensuing chronic lung disease and colonisation with *Aspergillus fumigatus*. Initially diagnosed with autosomal dominant Hyper IgE syndrome, this was later discounted after genetics demonstrated a mutation in IRAK-4 (c.877C>T, p.Q293X)[6]. This mutation had previously been reported, in both homozygous or compound heterozygous states, in 22 of 48 patients with IRAK-4 deficiency and in the patient reported in our case[1]. Notably, in our patient's final infection, she developed high fever and significantly elevated blood inflammatory markers, suggesting at least partial reversal of the classical paediatric IRAK-4 deficiency phenotype. However, we feel that the underlying immunodeficiency ultimately led to the infection given the rarity of fatal meningitis in the immunocompetent population.

There have been several isolated case reports and small case series reporting deaths solely in the paediatric cohort. To our knowledge, no deaths have been reported to date in adults. Therefore this case highlights the potential ongoing risk of fatal infection into adulthood. We recommend antimicrobial prophylaxis i.e. Penicillin V, should be continued at least until immunological evaluation has been fully completed. In addition if patients are not on immunoglobulin replacement therapy then they should be vaccinated against encapsulated bacteria, in particular pneumococcus and meningococcus as per nationwide/local guidelines and post vaccination responses assessed. Patients with IRAK-4 deficiency should commence prompt treatment with broad spectrum antibiotics at the onset of any symptoms suggestive of acute infection even if inflammatory markers are within normal parameters.

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