Understanding PANS & PANDAS

The interplay of immune system & mental health

By Micaela Monteiro-Haig

Insomnia, out-of-control tantrums, separation anxiety, rage, obsessions, disordered eating, paranoia, motor and vocal tics.

As a therapist or parent, have you come across a child exhibiting any of these behaviours and wondered if there was more to it than psychosocial, developmental or family dynamic issues at play? Have you known a child who used to be a great student but is now barely coping with school work because they can't focus, and has difficulty processing or remembering what they have learnt? Have you been left frustrated at the poor response to treatment? If so, you may have met or know a child who has paediatric acute-onset neuropsychiatric syndrome (PANS) or paediatric autoimmune neuropsychiatric disorder associated with streptococcal disease (PANDAS).

Unfortunately, most children with PANS/PANDAS are misdiagnosed as having psychiatric illness, behaviour problems, or parenting/family dynamic concerns. Many go through a number of psychiatric medications and therapies with minimal improvement, and many progressively get worse. A diagnosis of PANS or PANDAS should be considered whenever symptoms of OCD, tics, and eating restrictions start suddenly and are accompanied by other emotional and behavioural changes, frequent urination, motor abnormalities and/or handwriting changes (Calaprice, Tona, & Murphy, 2017). PANS/ PANDAS is also characterised by a relapse and remission pattern—children with PANS/PANDAS seem to have dramatic ups and downs in their symptoms, and an increased severity of symptoms is often correlated to a return of infection (PANDAS Physicians Network, 2017).

PANDAS and PANS describe a subset of paediatric onset obsessive compulsive disorder (OCD). PANS may also be a subset of avoidant/restrictive food intake disorder (PANDAS Physicians Network, 2017). It is considered a neuroinflammatory encephalitis that can have a number of infectious and non-infectious triggers (O'Hara, 2015). The syndrome is thought to be an immune reaction to various physiological stressors that include infectious agents such as group A streptococcal, mycoplasma pneumonia, influenza, human herpesvirus 6 (HHV-6), herpes simplex virus (Type 1 and 2), parvovirus B19, coxsackievirus, Lyme disease, Epstein–Barr virus, cytomegalovirus and candida (Song, 2017). Non-infectious agents include certain metabolic conditions (diabetes, lupus cerebritis), hormonal changes, environmental exposure to heavy metals, mould toxins, and psychological stressors (O'Hara, 2015). PANDAS is a subset of infection-triggered PANS caused by streptococcal infection (Calaprice et al., 2017). PANS and PANDAS symptoms can vary and do not necessarily present with an acute and dramatic onset (Song, 2017). Not rare, but rarely diagnosed due to poor awareness, it is estimated that 1 in 100 children are affected by PANDAS/PANS (Song, 2017). By definition, PANDAS is a paediatric disorder typically first appearing in childhood from age 3 to puberty; however, it is possible that adolescents and adults may have immune-mediated psychiatric disorders such as OCD (Autoimmune Encephalitis Alliance, 2016). The combination of autoimmunity and behaviour is a relatively new concept linking the brain, behaviour, and neuropsychiatric disorders with infections and immune activation (Cunningham, 2014).

The bacteria associated with PANDAS are known

as group A beta-haemolytic streptococcus (GABHS). Sites of streptococcal (strep) infection include: the throat, tonsils, adenoids, skin (eczema, psoriasis), urinary tract, gastrointestinal tract, and sinuses. In addition, rheumatic fever, a disease characterised by heart and joint inflammation, can also occur after an untreated strep throat (Cunningham, 2014). A child with PANDAS may not necessarily manifest with a sore, infected throat. At times, the only symptom may be a stomach ache, a rash or recurrent impetigo, or a persistent sinus or ear infection (O'Hara, 2015). Comprehensive testing, with throat, nasal, ear, and perianal swabs, as well as blood antibody titres against strep antibodies, is recommended, and a viral and bacterial panel is also advisable (Song, 2017). In PANDAS, GABHS antibodies persist for several years after the streptococcal infection occurs (Nicolini et al., 2015). Although strep antibody titres may not always be elevated, this does not exclude a diagnosis of PANDAS (Cooperstock, Swedo, Pasternack, & Murphy, 2017).

Pathophysiology

The proposed theory for PANS and PANDAS postulates that serum antibodies produced against infectious and non-infectious agents cross the blood–brain barrier (BBB) and cross-react with neuronal antigens (Pearlman, Vora, Marquis, Najjar, & Dudley, 2014). These antibodies then elicit injury and cause dysregulation to basal ganglia functions producing a variety of neurological and psychiatric manifestations (O'Hara, 2015; Pearlman et al., 2014). Anti-neuronal antibodies produced include anti-lysoganglioside, anti-tubulin, and anti-dopamine D1 and D2 receptor antibodies (Cunningham, 2014). Their effects on the brain include alterations to the enzyme tyrosine hydroxylase, resulting in increased synthesis of dopamine (O'Hara, 2015). In addition, dopaminergic and glutamatergic transmission and regulation are affected due to an increase in receptor sensitivity caused by antibody stimulation (O'Hara, 2015). Increased dopamine and glutamate in the basal ganglia may be respon-

sible for the overstimulation and the many psychiatric symptoms associated with PANDAS.

The autoimmune pathophysiology of PANS and PANDAS may result not only from the adverse effects of neuronal antibodies but also from the promotion of inflammatory mediators such as neuroactive cytokines (Calaprice et al., 2017). A role for inflammatory mediators in psychiatric illness has been identified in both children and adults (Baumeister, Russell, Pariante, & Mondelli, 2014; Mitchell & Goldstein, 2014). In addition to their direct action in certain areas of the brain, inflammatory mediators in PANDAS/PANS have also been implicated in a breach of the BBB by inducing capillaries to expand and allowing the tissues to become more permeable (Calaprice et al., 2017). When this occurs, it makes the BBB vulnerable to the entry of pathogens, permitting neuroactive antibodies to reach neuronal tissue (Calaprice et al, 2017). Of note, research has demonstrated neuroinflammation within the neurocircuitry and pathophysiology of OCD (Attwells et al., 2017; Giedd, Rapoport, Garvey, Perlmutter, & Swedo, 2000; Kumar, Williams, & Chugani, 2014).

Neurons connecting to the basal ganglia affect motor function, emotion, behaviour, procedural learning, cognition, and sensory issues. Neurological and psychiatric manifestations include: OCD, mood lability, depression, mania, irritability, sleep disorders, anxiety (frequently presenting as generalised anxiety or age-inappropriate separation anxiety), rage, developmental regression, hypersexuality, hyperactivity, inattentiveness, oppositional behaviours, obsessive thoughts, checking behaviours, poor muscle control or coordination, new-onset bedwetting, handwriting changes, clumsiness, tics, choreiform movements, cognitive impairment (e.g., slow processing, poor memory, specific sensory learning deficits, particularly in maths and tasks involving calculation), sensitivity to light, sounds, tastes, smells and textures (PANDAS Physicians Network, 2017). In addition, the PANS/PANDAS child may exhibit a fear of vomiting or of being poisoned or contaminated (O'Hara, 2015). This often

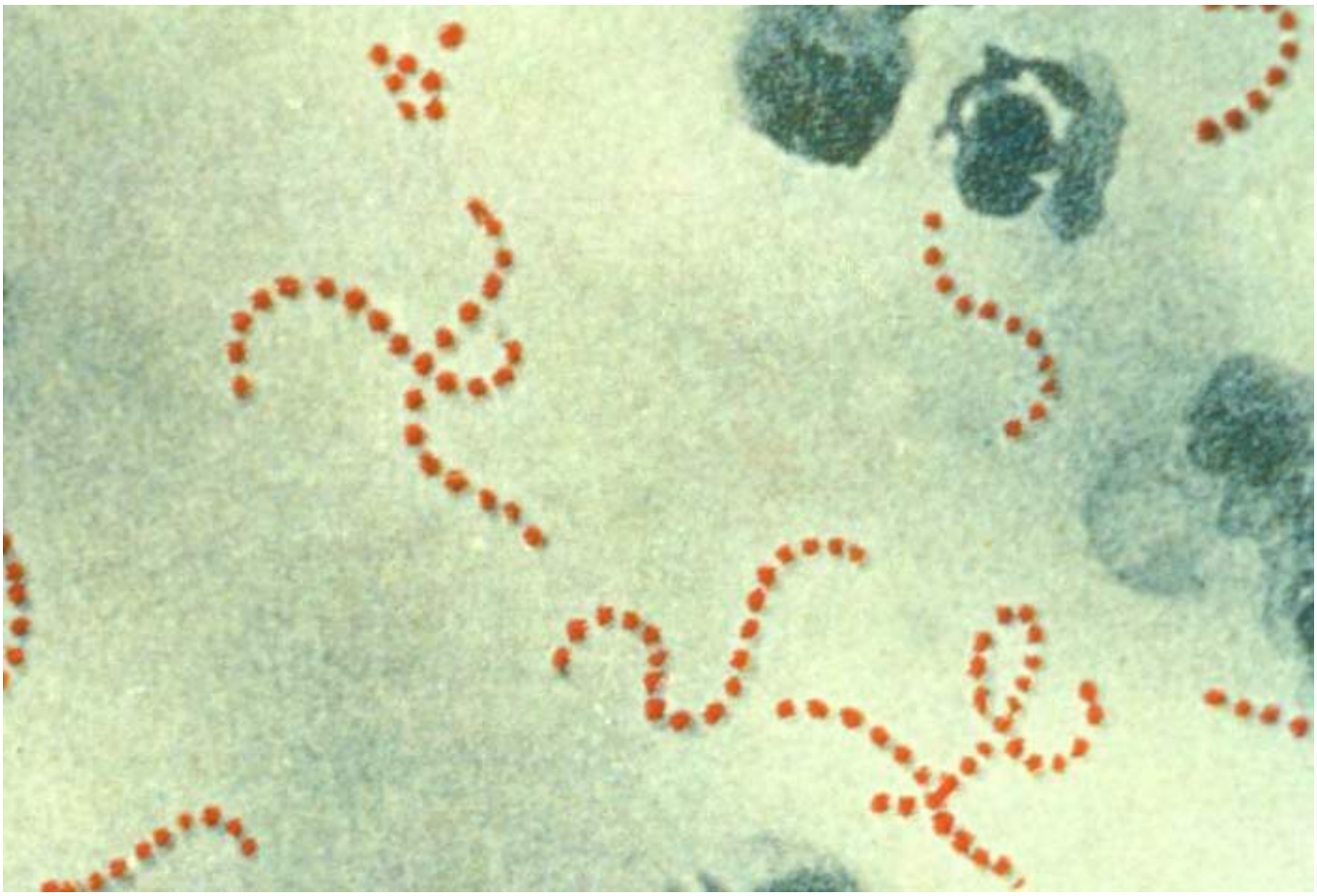
leads to difficulties with daily activities such as eating, going to the toilet, going in a car, and dressing. Tics can include uncontrollable movements such as eye-blinking, hair twirling, lip smacking or shoulder shrugging, or automatic noises such as throat clearing, grunting, or saying certain words repeatedly (PANDAS Physicians Network, 2017).

The impact of PANDAS/PANS is further exacerbated by certain individual vulnerabilities such as a family history of autoimmune disease, a compromised immune system, impaired detoxification pathways and pyrrole disorder, to name a few.

Due to the nature of a long-standing infection, individuals with PANDAS/PANS will often present with other issues that require attention. An overactive immune system and persistent infection as seen in children with PANDAS/PANS exerts an increasing strain on the stress response and the hypothalamic-pituitary-adrenal (HPA) axis (Gruner & Sarris, 2014; Silverman & Sternberg, 2012). Children with PANDAS/PANS will often have increased stress hormone levels further exacerbating the condition; increase in the stress hormone cortisol, and persistent inflammatory cytokine release, will in turn affect sleep and mood via disruption to serotonin production in the brain (Gruner & Sarris, 2014; Savitz et al., 2015). As this neurotransmitter exerts a modulatory effect on dopamine, lower levels of brain serotonin further exacerbate the effects of dopamine dysregulation in neuronal circuits. Continued disruption in HPA-axis function due to ongoing infection can eventually lead to underproduction of cortisol and other stress hormones (Gruner & Sarris, 2014). This can result in poor stress tolerance, fatigue, sleep issues, and increased susceptibility to other infections (Gruner & Sarris, 2014).

Treatment

Treatment of PANDAS/PANS requires a multipronged approach where a number of modalities are employed in order to address the cause (or causes) and resolve symptoms. Comprehensive treatment delivered by a team of specialists (including paediatric neurologists and psychiatrists, psychotherapists, occupational therapist and naturopath/nutritionist,



dependent on the severity of the case) will give the PANDAS/PANS child the best chance of remission. Generally, the clinical management and treatment of PANDAS/PANS will comprise behavioural and pharmacological interventions that include antibiotic therapy (often for a period of months or years), immunomodulatory and/or immunosuppressive therapy, psychotropic medication, cognitive behavioural therapy, and family therapy (Thienemann et al., 2017). However, as functional medicine practitioner and paediatrician Elisa Song (2017) has noted, while psychotropic medications may be needed during crises, they are a bandaid solution and are often not effective until the underlying causes are addressed. Most children who undergo treatment show overall improvement over months and years, although relapses may still occur after long periods of remission (Cooperstock et al., 2017).

The focus of treatment should be on each individual child and not a protocol, as symptom presentations differ. Within individualized treatment, however, there is a framework that encompasses dealing with any active infection, addressing the underlying inflammation, modulating the immune system, and supporting the child through the process of flare-ups. Additionally, therapies that support brain and central nervous system function and regeneration, modulate the HPA axis, address nutrient deficiencies (as a consequence of disordered eating) and support gut health, as well as other organs and systems affected, are paramount.

Complementary medicine in the treatment of PANDAS/PANS has been shown to be helpful, with a high use among patients (Calaprice et al., 2017). The most frequently used treatments include dietary modifications (comprising an anti-inflammatory diet), supplements that include probiotics to support the gut microbiome and gut–brain connection (especially important during antibiotic treatment), vitamin D as an immunomodulatory agent, fish oils (or other omega-3 fatty acids), turmeric/curcumin, vitamin C, melatonin and N-acetylcysteine for reducing oxidative stress and inflammation, B vitamins, magnesium, zinc, broccoli sprout powder and glycine to improve detoxification pathways, and CoQ10, acetyl-carnitine and ribose to address mito-

chondrial dysfunction (Calaprice et al., 2017; O'Hara, 2015). Further to the above, other interventions include herbal agents with immunomodulatory and/or immunosuppressive actions to optimise immune function and decrease the autoimmune response (Bradbury & Hartley, 2014).

The prognosis for a child with PANDAS/PANS depends to a great extent on appropriate diagnosis of the disease and early intervention. It is vital that any child exhibiting symptoms of PANDAS/PANS be referred for proper and comprehensive testing and appropriate treatment. Only then is recovery possible.

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