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Sydenham's Tourettic PANDAS??!
Bringing the Most Recent Data to Bear In Carving Nature at its Joints

July 6, 2000.

Following an outbreak of streptococcal infections on Rhode Island in 1991, Dr. Louise Kiessling observed that strep infections seemed to precipitate the onset of tic disorders (TSA, 1993; in Kushner & Kiessling, 1993; Kurlan, 1998). The subsequent link made between alpha beta hemolytic streptococcal infections and neurological sequelae, evidence for which had already appeared sporadically within the literature (Kondo & Kabasawa, 1978; Matarazzo, 1992) was a valuable display of reciprocal transaction in the medical literature. Rather than engaging in fruitless and tired debates over whether a particular disorder's etiology lies in "nature" or "nurture", neurology or psychology, both environmental trigger and neurological diathesis could readily be seen to interact and influence one another in the development of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS).

Now that PANDAS has been established and verified as a diagnosis, however, discussions now turn to the question of where PANDAS fits in the context of other syndromes and disorders with similar collections of symptoms. Is PANDAS similar enough to other manifestations of rheumatic fever (such as Sydenham's Chorea; SC) to be subsumed under this? Are all instances of disorders such as Tourette Syndrome (TS) and Obsessive-Compulsive Disorder (OCD) subsumed under the label PANDAS – is PANDAS simply our first clear etiological delineation of these conditions? Or are all three (SC, PANDAS, TS) unique diagnoses unto themselves? While definitive answers to these issues are yet to be found, the elucidation of how at least a subset of the population experiencing tics, obsessions, and compulsions have come to develop these symptoms brings whole new perspectives on prevention and treatment to attention.

Scientists have known since the early 1960's of the connection between opportunistic childhood streptococcal infections and SC (Kushner & Kiessling, 1993). Although at the time considerable opposition to this idea was raised, the suggestion that Group Alpha beta hemolytic streptococcus infection (GABHS) elicits antibodies that cross-react with the basal ganglia to produce involuntary movements and abnormal behaviours in SC is widely recognized today (Garvey, Giedd, & Swedo, 1998). It is believed that the GABHS infection leads to rheumatic fever in about 2-3% (Murphy, Goodman, Ayoub & Voeller, 2000), usually within 20 days. The fever manifests with inflammation of the heart (carditis), joints (arthritis), and brain. Two to six months following the infection, SC then manifests in ballismus, facial grimacing, fasciculations of the tongue, fine motor control loss, hypotonia, motor impersistence, gait disturbance, and speech abnormalities (Kurlan, 1999; Murphy, Goodman, Ayoub & Voeller, 2000). How exactly the antibodies are able to permeate the bloodbrain barrier (BBB) to cross-react with the basal ganglia is not precisely known; it has been suggested that immunologic stress may cause increased permeability of the BBB, thus allowing antineuronal antibodies to pass (Kurlan, 1998).

In the last decade, evidence has begun to accumulate to suggest that this same basal ganglia autoimmunization may also be a trigger for many movement disorders in genetically predisposed individuals causing tics and/or obsessive-compulsive symptoms. Rather striking is the finding by Singer, Giuliano, Hansen et al. (1998) that the mean levels of serum antibodies found to be increased in a TS sample were those against putamen, and that antibodies specific to the caudate and putamen occurred more frequently in TS individuals: the various cortico-striato-thalamo-cortical (CSTC) circuits implicated in TS all involve the caudate or putamen (Rauch, 1999;

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Sawle, Lees, Hymas, et-al 1993). As well, while the precise neurological abnormalities associated with TS remain debatable, an overwhelming number of the studies implicate either the putamen or caudate (Wolf, 1996; Malison et al., 1995; Riddle et al., 1992; Moriarty, 1995). These and other discoveries have prompted a parallel conflict in the scientific community (Garvey, Giedd, & Swedo, 1998). One of the biggest matters to address is how do we alter our current diagnostic practices to accommodate this new knowledge. What if any new categories do we create, and what if any categories are now rendered obsolete?

Is PANDAS a Subtype of Sydenham's Chorea?
Unlikely. In at least one study, those in the PANDAS sample were screened carefully for signs of rheumatic fever using the Jones criteria; no typical manifestations were found (Swedo, Leonard, Mittleman, et al., 1997). For example, there is no evidence of brain inflammation and the resulting delirium in PANDAS cases. There is also no evidence to suggest that individuals with TS suffer an increased incidence of cardiac disease (Murphy, Goodman, Ayoub & Voeller, 2000). It is even debated whether true chorea (brief, arrhythmic, "dancing" movements) is seen in the PANDAS population (Kurlan, 1999; Swedo, Leonard, Mittleman et al., 1997); currently PANDAS will not be considered as a diagnosis if chorea is present (Murphy, Goodman, Ayoub & Voeller, 2000).

It seems more likely that PANDAS and SC are both distinct manifestations of a similar underlying streptococcal autoimmunity. Swedo, Leonard, Mittleman, et al. (1997) conducted a study to determine whether children diagnosed with PANDAS could be identified by the same marker as for rheumatic fever susceptibility (D8/17, found on DR+ cells in the peripheral circulation). Compared to controls (who were D8/17 positive only 17% of the time), those diagnosed with PANDAS were significantly more likely to carry this marker (85% were D8/17 positive). Moreover, the percentage of positive carriers in the PANDAS population was quite similar to that of a population of children diagnosed with SC (89%; Swedo, Leonard, Mittleman, et al., 1997). This latter finding should be viewed cautiously however, as the n for the SC sample was only a third of the PANDAS sample. The authors go on to postulate that different genetic vulnerability, neurodevelopmental maturation, and host-microbe interaction specificity may account forthe different responses to GABHS in the two populations.

Is TS a Subtype of Sydenham's Chorea?
Interestingly enough, the original observers of TS (such as Itard) actually resisted the formation of a category for these cases separate from general choreas (Kushner & Kiessling, 1993). While in general terms tics are distinct from chorea, it is not uncommon for individuals with SC to exhibit some motor and phonic tics, and individuals with TS may show chorea-like movements (Murphy, Goodman, Ayoub & Voeller, 2000). Streptococcal M proteins (particularly M12) evoke an autoimmune response in neurons of the basal ganglia in SC: antibodies against M12 proteins were also found to be significantly increased in a sample of TS individuals (Mûller, Kroll, Schwarz, et al, poster A). In addition, increased titers of antistreptococcal antibodies were found in children and adolescents with TS as compared to controls (Mûller, Riedel, Straube, et al, poster). Kiessling, Marcotte, and Culpepper (1993) further note that the percentage of children in their sample with a high quantity of antineuronal antibodies was very similar to the percentage found in children with SC (44% vs. 46%).

Despite the similarities between TS and SC, there are some important differences. While it was widely believed that the involuntary movements observed in both chorea and what was to be eventually called TS in all likelihood shared a common pathology, the latter, like PANDAS, did not exhibit any delirium or signs of rheumatic fever (Kushner & Kiessling, 1993). Another problem is that symptoms SC has in common with TS usually resolve themselves within one or two years (Kiessling, 1997). TS tends to be considerably longer in duration, first diagnosed before the age of 11 in 96% of cases (Robertson, 1989) and lasting until at least late

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adolescence (Goetz, Tanner, Stebbins et al. 1992). New research has even questioned whether in the majority of cases tics DO resolve in early adulthood – it now seems more likely that the majority of people with TS can expect to have some level of tic activity throughout life (Goetz, Tanner, Stebbins, et al. 1992). Based on the available evidence, it seems safe to assert that Charcot and Tourette acted appropriately in discriminating the diagnoses of TS and SC.

Is TS a Subtype of PANDAS?

Neither PANDAS nor TS seem to fit the Sydenham's Chorea label well; while the evidence of high levels of a ntineuronal antibodies in both groups has been well replicated (for example, Kiessling, Marcotte, & Culpepper, 1993), the symptoms that individuals with TS and PANDAS experience are of considerably longer duration than those seen in Sydenham's Chorea, and do not include any symptoms of rheumatic fever. Perhaps, though, TS and PANDAS are one and the same.

At first blush, the TS cases subsumed within the PANDAS diagnosis do not appear to differ from TS cases in general. Judging from PANDAS samples taken from Swedo, Leonard, Mittleman et al. (1997) and Garvey, Perlmutter, Allen, et al. (1999), similar sex ratios (more boys to girls), incidences of "pure" TS (tics without comorbid diagnoses), and incidences of comorbid OCD and ADHD appear in both PANDAS and TS populations (Fast & Freeman, 1997; Robertson, 1989). Average age of onset for both PANDAS and TS are similar (Murphy, Goodman, Ayoub & Voeller, 2000). Furthermore, both TS and PANDAS follows a waxing and waning course (it was thought at one time that PANDAS was distinctively episodic; more recent descriptions have turned from this notion), and it is put forward that while greater awareness of TS may be creating the illusion of increased incidence, a very real incident increase may be occurring due to the development of more virulent strains of GABHS (Kurlan, 1998). Children with tics were 4 to 6 more lkely to have evidence of streptococcal infection, and to have serological (blood) antibodies to central nervous system cells (tested on caudate sections; Kiessling, Marcotte, & Culpepper, 1993). This finding was replicated by the same authors. Individuals with TS symptoms have been found to carry the same marker as that found in rheumatic fever on their β-lymphocytes, known to be caused by infection by alpha-beta hemolytic streptococcus (Swedo, Leonard, Mittleman, et al. 1997). Finally, a recent study by Kleinsasser, Misra, Bhatara, and Sanchez (1999) documented the effective treatment of a PANDAS case with risperidone, a neuroleptic well documented to be effective in the treatment of TS (for example, Zhang 1999 poster).

There are problems with considering all cases of TS to be included beneath the PANDAS construct. The diagnostic criteria for PANDAS, while somewhat of a "moving target" (Murphy, Goodman, Ayoub & Voeller, 2000), are currently a virtual mirror of TS. They are as follows: the presence of a tic disorder with pediatric onset, an episodic course, neurological, psychological (such as impulsivity) and cognitive (such as distractibility) abnormalities, and finally the presence of comorbid psychiatric difficulties including but not limited to Attention-Deficit Hyperactivity Disorder (ADHD), Conduct Disorder, mood disorders, and anxiety disorders (Kurlan, 1999; Swedo, 1999). The only unique criterion is that of temporal association of tics subsequent to a strep infection (Kurlan, 1998). When one defines PANDAS using all TS criteria it is hard for them NOT to appear similar. This seems somewhat self-fulfilling. Despite this similar criteria, evidence is mounting that TS is not restricted to childhood and adolescene (Robertson, 1989; Goetz, Tanner, Stebbins, et al. 1992), although PANDAS by definition is.

There is more than one explanation for why one might expect to see an increase of tic symptoms following a strep infection other than a causal one. For instance, it could be a simple non-specific stress response: TS literature has documented the exacerbating effect stress has on tics (Robertson, 1989). This brings up the

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important caveat that correlation does not equal causation.

Perhaps an even more fatal blow comes in the discovery that the relationship between the presence of antineuronal antibodies and tic symptoms is not a clean one. Elevated neuronal antibodies cited so frequently in the literature are missing in some individuals with TS; likewise they are present in some controls without a tic disorder being present (Kurlan, 1998). Exacerbations in tic severity have been seen without concomitant GABHS infection (Murphy, Goodman, Ayoub & Voeller, 2000). Moreover, there appears to be no relationship between level of antineuronal antibodies and tic severity.

It seems then while we can tentatively conclude that perhaps a subset of individuals currently diagnosed with TS may be best considered PANDAS patients there are some with TS that remain distinct from this category. In a recent review of the data, 10-20% was an agreed on figure for several groups (Trifiletti & Packard, 1999; Murphy, Goodman, Ayoub & Voeller, 2000). Potential red flags for identifying the PANDAS subset of TS cases could be acute and dramatic onset, a relapsing-remitting symptom pattern, and a preceding GABHS infection or exposure, or pharyngitis or upper respiratory infection (Swedo, Leonard, Garvey et al. 1998).

Repercussions for prevention/treatment

The study of PANDAS provides a real opportunity to move further "upstream" in the understanding and remediation of certain cases of TS: armed with the knowledge of how and through what process this pathology appears, clinicians are equipped to act much more proactively.

At best, if a subgroup of TS patients is found to have their pathology triggered by GABHS, the opportunity arises to screen vulnerable individuals and prevent the onset of symptoms. Weiss and Garland (1997) warn that positive antistreptolysin O (ASO) titers were rarely associated with positive throat culture results in their client (Weiss & Garland, 1997), suggesting that individuals being assessed for tic disorders should be routinely checked for abnormally high antineuronal antibodies whether or not their history includes sore throats.

At worst, if an increase in tics following a strep infection only represents a non-specific stress response, preventing and/or treating that stressor will have beneficial effects in that exacerbations of the existing disorder will be minimized. In a case study report, Weiss and Garland (1997) note that treatment with amoxicillin was followed by a return to baseline symptoms, although trials of thioridazine, alprazolam, paroxetine, risperidone, clonidine, haloperidol, and sertraline each produced questionable improvements at best.

For those TS cases not responsive to traditional (dopamine-antagonist neuroleptics) treatment, this new research could provide a possible new avenue for treatment (Kurlan, 1999 symposium), although further work in this area still needs to be done. Intravenous immune globulin (IVIG), plasmapherisis, and penicillin have all been claimed beneficial in treating acute, severe PANDAS (Swedo, 1999 symposium), although Kurlan (1998) points out that many of these studies have not been controlled. Garvey, Perlmutter, Allen et al., the following year, published a well-controlled, double-blind, balanced cross-over study on the use of penicillin prophylaxis in the treatment of PANDAS. Startlingly, the investigators found no change in tic severity between placebo and drug trial phases (Garvey, Perlmutter, Allen et al., 1999).

Finally, this research may also have similar repercussions for OCD and ADHD, as these two disorders often co-occur with TS, and both may share similar genetic heritages – namely an exaggerated reaction to GABHS infections, leading to altered neuroanatomical circuitry. The degree to which the PANDAS construct should be widened to accommodate these other disorders is yet to be determined (Murphy, Goodman, Ayoub et al., 2000).

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Available evidence leads to the conclusion that PANDAS accounts for a subset of individuals diagnosed with TS, and possibly other disorders such as OCD and ADHD. PANDAS itself seems to share a similar etiology with SC, but is best considered as a separate condition. Future work in the area of PANDAS will no doubt be fruitful and exciting, for within the pursuit of increased understanding of this causal pathology arises the potential to minimize, alternatively treat, or prevent tic symptoms in some individuals with TS altogether.

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