CMLS, Cell. Mol. Life Sci. 61 (2004) 886–898
1420-682X/04/080886-13
DOI 10.1007/s00018-003-3320-4

CMLS Cellular and Molecular Life Sciences

Review

Neurobiology and neuroimmunology of Tourette's syndrome: an update

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Received 12 August 2003; received after revision 8 October 2003; accepted 31 October 2003

Abstract. Tourette's syndrome is a childhood-onset neuropsychiatric disorder characterized by the presence of both multiple motor and vocal tics. While the pathogenesis at a molecular and cellular level remains unknown, structural and functional neuroimaging studies point to the involvement of the basal ganglia and related cortico-striato-thalamo-cortical circuits as the neuroanatomical site for Tourette's syndrome. Moreover, Tourette's syndrome has a strong genetic component, and considerable progress has been made in understanding the mode of transmission and in identifying potential genomic loci. Summaries of recent findings in these areas will be reviewed, followed by a critical overview of findings both supporting and challenging the proposed autoimmune hypothesis of Tourette's syndrome. We conclude that Tourette's syndrome is a heterogeneous disorder, and that immune factors may indeed be involved in some patients.

Key words. Tic disorders; magnetic resonance imaging; emission-computed tomography; dopamine; genetics; streptococcal infections; autoantibodies; autoimmunity.

Introduction

A tic is an involuntary, sudden, rapid, recurrent, nonrhythmic, stereotyped motor movement or vocalization [1]. Thus, a distinction is made between motor and vocal tics. Tics are rather common in school-age children, but are more often than not transient phenomena [2]. They may, however, follow a chronic course, and can be present lifelong in some persons [3]. The best-studied tic disorder is Tourette's syndrome (TS), defined in the latest edition of the 'Diagnostic and Statistical Manual of Mental Disorders' (DSM-IV TR) [1] by the presence of both multiple motor tics and one or more vocal tics throughout a period of more than 1 year, during which period there was never a tic-free period of more than 3 consecutive months. Closely related [4] are a number of other tic disorders as defined in DSM-IV TR, most notably chronic motor tic disorder and chronic vocal tic disorder, in which only one type of tic is present, either solely motor movements or vocalizations, respectively.

While tic disorders were once regarded as psychogenic conditions [5], twin and family studies now indisputably point to a major genetic contribution in these disorders. Neurobiological research has revealed a number of possible alterations, and there is some indication that immune dysregulation may be involved in the pathogenesis of tic

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disorders. Briefly, some of the immune research suggests that infections may induce or reinforce tics and associated features in susceptible individuals, through the possible involvement of abnormal humoral immune responses directed against self tissue antigens. After outlining the main clinical features of TS and summarizing the research in the areas of genetics, neurochemistry, and neuroimaging, we will present an overview of findings supporting, as well as challenging, the immune hypothesis of tic disorders.

Clinical features

Tics vary greatly between and within individuals. Most motor tics are brief, sudden, and meaningless muscle movements, such as eye blinking, nose twitching, or shoulder shrugging, referred to as simple motor tics. In contrast, complex motor tics appear more purposeful and involve several muscle groups. Examples include touching other people or objects, retracing steps when walking, and various complex hand gestures. Similarly, vocal tics may be subdivided into simple and complex tics, ranging from meaningless sounds such as throat clearing, sniffing, and barking to the sudden utterance of words, phrases, and full sentences which may include echolalia and coprolalia. Tic intensity can vary substantially, ranging from barely visible or audible tics to extremely forceful or loud expressions. Quite often, tics are mild, in which case they may hardly attract attention from others and may not interfere with everyday life at all. However, powerful and frequent tics may severely interfere with everyday activities, including speech, driving, and walking. In exceptional cases, tics may lead to physical injury, including joint dislocation and other tissue damage. Patients who display more severe or complex tics may be stigmatized as a result of the unusual, inappropriate, and bizarre character of their tics.

Most patients do not experience their tics as entirely beyond their control [6]. Many individuals describe premonitory urges preceding their tics [7], feelings that are momentarily relieved by the performance of tics and may be temporarily ignored by suppressing the tics. Furthermore, tics tend to occur in bouts alternated with relatively tic-free periods within the course of a day [8].

The median age of onset of tics is 7 years [9]. Onset before the age of two and after the age of twelve is highly unusual. Cases of adult-onset of tics, however, have also been described [10]. In general, tics do not start abruptly in an individual's life. More typical is a gradual initial course, in which weeks with mild tics alternate with tic-free periods. Over time, tics may either disappear spontaneously or may gradually become more frequent and prominent. Initial tics almost invariably involve the face; most frequently, eye blinking forms the first tic symptom. In the following months to years, tics may spread to other body parts and may become more complex and forceful. Vocal tics tend to begin several years after the first motor tics have appeared. They commonly start as meaningless simple sounds, but may be supplemented by more complex vocalizations later on. Especially in children, tics tend to vary substantially over time in their location, frequency, and forcefulness, and may typically follow a waxing and waning course with regard to overall severity [11]. This changing pattern tends to become less varied by the early adult years, concomitant with an overall trend of diminishing tic severity [12], with regard to both intensity and frequency. Still, a significant minority of patients may continue to demonstrate bothersome tics in their adult years.

A recent large epidemiological study reported transient tics to be present in up to 5% of school-age children, and reported a prevalence of TS in school age children of about 0.6%, with males found to be more frequently affected than females [2]. This prevalence of 0.6% is higher than those reported in most previous studies [13], but is in accordance with a recently identified minimum prevalence of TS amongst 13–14 year olds of 0.76% [14], and lower than one previous study reporting that 3.8% of schoolchildren met diagnostic criteria for TS [15].

A final important feature of tic disorders is their association with a wide range of comorbid behavioral abnormalities, which in certain individuals may be more clinically relevant than the tics themselves. Most studies have reported increased frequencies of hyperactivity, impulsivity, attentional impairments, obsessive-compulsive features, and difficulties regarding social functioning in tic disorder patients, when examined on a group basis [16– 18].

Neuroanatomy

Currently, the pathogenesis of tic disorders at a molecular and cellular level is unknown. Also, there is no definite evidence of the neuroanatomical substrate of tics. The basal ganglia play an established role in other movement disorders, including Huntington's disease [19], Parkinson's disease [20], and encephalitis lethargica [21], and, thus, form an attractive candidate site for involvement in tic disorders. Moreover, based on the phenomenology and natural history of tic disorders, cortico-striato-thalamo-cortical (CSTC) circuits have been suggested to be involved in tic disorders [22]. At least five functionally and anatomically distinct CSTC circuits have been identified, which subserve sensorimotor, motor, oculomotor, cognitive, and limbic processes (recently reviewed by Mink [23]). A failure to inhibit specific CSTC circuit subsets has been hypothesized to be involved in tic and related disorders, and may be directly linked to specific types of tics, given the somatotopical organization of these CSTC circuits. For example, facial tics could be as-

sociated with a failure of inhibition of CSTC circuits that include the ventromedian areas of the caudate and putamen and that receive topographical projections from the orofacial regions of the (pre)motor cortex. Similarly, oculomotor CSTC circuits may be involved in eye movement tics, whereas the limbic circuit may be associated with vocalizations and comorbid obsessive-compulsive disorder (OCD) and externalizing behavior problems [23].

The possible involvement of the basal ganglia and related cortical structures in tic disorders is supported by recent large-scale structural magnetic resonance imaging (MRI) studies involving both children and adults with TS. These have identified basal ganglia and cortical volume differences between TS patients and healthy controls [24, 25]. Basal ganglia volumes [25] were not found to correlate significantly with the severity of tics. In contrast, regional orbitofrontal, midtemporal, and parieto-occipital volumes were significantly associated with the severity of tic symptoms [24]. In addition, some studies identified evidence for increased interconnecting structures in the corpus callosum [26, 27], whilst a different study [28] reported a decreased total corpus callosum midline cross-sectional area. Also, previously [23–25] reported findings in small samples of a lack an inversion of normal basal ganglia volume left-right asymmetry could not be replicated in larger samples [25]. However, across both children and adults with TS, volumes of the caudate nucleus were found to be significantly reduced [25]. Previously, in a study involving monozygotic twins both affected with TS, the caudate nucleus was also consistently found to be smaller in the more severely affected co-twin [31], which points to the nongenetic nature of the identified caudate volume reduction. The most prominent feature of the recent large-scale studies [24, 25], though, was strikingly different findings between children and adults with TS. In accordance with previous work [29], adults with TS were found to have reduced lenticular nuclei volumes, which was not observed in children with TS [25, 30]. Similar remarkable differences between children and adults with TS were reported with regard to cortical volumes [24]. Prefrontal and orbital frontal cortical volumes were enlarged in children with TS, but decreased in adult patients, compared with healthy controls. It should be stressed, though, that the precise functional meaning of reported brain volume alterations in TS is unclear. Also, neuroanatomical findings may have been partially obscured by the presence of behavioral comorbidities. Finally, in a functional MRI study in which adult patients were asked to suppress their tics, prefrontal areas were found to be strongly activated [6].

Taken together, the structural MRI studies certainly support the involvement of the basal ganglia and interconnected cortical structures. To illustrate this, specific CSTC circuits are known to terminate in the caudate nucleus [23], which is consistently found to be smaller in TS patients. Still, the identified volume differences may not necessarily be directly related to the pathophysiology of TS [32]. When considering the opposing direction of some of the neuroimaging findings in children and adults with TS, it should be remembered that adults who continue to show tics do not represent the typical course of tic disorders. Rather, the majority of TS cases have shown complete remission by the early adult years. Thus, adults with tics may form a subgroup that is unsuccessful in finding compensatory pathways to the tics. Accordingly, identified volume changes in children with TS may actually reflect such compensatory pathways, pathways that the adults with tics would not be expected to display. In other words, volume changes may point to the plasticity of the brain in response to compensating for the presence of tics, rather than form a direct expression of the pathogenesis of tics. Again, it should be stressed that the meaning of brain volume alterations remains speculative. Above all, these findings point to the importance of longitudinal MRI studies that could study volumes of relevant brain structures in relation to the onset, changing severity pattern, and possible remission of the tics over the course of time [32].

Finally, in general, findings of positron-emission tomography (PET) and single-photon emission-computed tomography (SPECT) studies are also in accordance with the involvement of the basal ganglia in TS. Both reduced glucose utilization in the ventral striatum [33–35], as well as reduced blood flow in the globus pallidus and putamen [36] or the entire basal ganglia [32, 38] have been reported. Also, these studies have shown widespread changes in cortical regions, with variable results even within the same institution [33, 34].

In addition, a recent PET study [39] compared regional cerebral glucose metabolic rates between TS patients and controls, and found altered limbic-motor interactions in TS, again pointing to the relevance of the CSTC circuits. Functional connections between the motor and lateral orbitofrontal circuits were identified in both patients and controls; however, a reversal in the pattern of these interactions differentiated TS patients and controls. In TS patients, activity in the motor and lateral orbitofrontal circuits appeared to be positively correlated, whereas in healthy controls increased activity in motor circuits appeared to be associated with relative inactivity in lateral orbitofrontal circuits [39]. The precise meaning of these alterations remains largely unknown. It should be noted that results from structural studies should not directly be interpreted in functional terms, e. g. PET/SPECT studies do not give information on receptor affinity.

Neurochemistry and psychopharmacology

Without doubt, altered neurotransmission is involved in the pathophysiology of tics. Central neurotransmitters

serve the major goal of communication within the brain, through binding to specific receptors. Several well-established research findings strongly suggest disturbances within the dopaminergic system in TS. First, dopamine receptor-blocking pharmacological agents constitute the most effective tic-suppressing medication [40]. Moreover, agents which increase central dopaminergic activity such as L-dopa [41] and CNS stimulants [42] may induce or exacerbate tics, even though more recent studies have indicated that certain stimulants, particularly methylphenidate and dextroamphetamine, do not generally increase tics [43]. Indeed, in five monozygotic twin pairs with TS, SPECT findings suggested increased dopamine receptor capacity in the caudate nucleus of the more severely affected co-twin [44], possibly explaining the beneficial effect of dopamine antagonists in tic disorders [40]. In addition, a recent PET study demonstrated increased intrasynaptic dopamine levels in the putamen of TS patients after amphetamine challenge, which the authors linked to possible abnormal dopamine transporter regulation in TS [45]. The latter observation can be taken to suggest that in TS patients dopamine neurons may release larger than normal amounts of the transmitter when activated, possibly resulting in loss of control of motor functions, and the emergence of tics. A recently reported animal model does tend to support a role for hyperactivation of the dopaminergic system. Transgenic mice expressing a neuropotentiating protein within a cortical-limbic subset of dopamine D1 receptor-expressing neurons were shown to demonstrate tic-like behavior [46].

A postmortem brain study has reported that neuronal dopamine uptake sites were significantly increased in number in the caudate and the putamen, compared with control values. This was suggested to indicate enhanced dopamine innervation within the striatum [47]. However, other postmortem brain studies have not found differences in a range of presynaptic dopaminergic markers [42, 49], and a large study of cerebrospinal fluid neurochemicals did not find altered levels of the principal dopamine metabolite, homovanillic acid [50]. Also, dopamine D2 and D3 receptor availability have not been found altered in PET [51, 52] and SPECT [53] studies. In addition, a PET imaging study of a presynaptic marker of dopaminergic neurons in the striatum did not find differences between TS and healthy controls [54]. Thus, currently there is no clear unified dopaminergic hypothesis in TS.

Limited additional neurochemical data are available which are suggestive of alterations of other neurotransmitter systems, including the noradrenergic [50] system, endogenous opioid peptides [55], the serotonergic system [49], and the glutamatergic system [49]. The report of altered glutamatergic neurochemistry in the medial globus pallidus is of interest, as it is consistent with imaging studies indicating alterations in the pallidum.

Genetics

TS has a strong genetic background (recently reviewed by Pauls in [56]). In a twin study, in which at least one co-twin had TS, it has been demonstrated that monozygotic twins are more often concordant for the presence of TS (53%) or any tics (77%) than dizygotic twins (8% concordant for TS and 23% for any tics) [57]. Thus, genetic factors play a profound role, but the phenotype may be variable and may not be confined to full-blown TS. Indeed, family studies have shown that family members of a proband with tics are much more likely to have tics, compared with persons in the general population [58, 59]. Several independent family segregation analyses have reported that the mode of vertical transmission of TS fitted best to a mode of inheritance involving a single autosomal dominant locus with varying penetrance [59–61], though more recent studies have indicated that the genetic transmission is probably more complex [62, 63].

Subsequent classic multigenerational parametric linkage studies were unsuccessful in finding the presumed major TS locus, after having excluded more than 95% of the genome [56, 64]. These linkage studies had been carried out under the assumption that TS is a homogeneous disorder in which a major dominant gene would be involved, and that the presumed TS phenotype would include chronic motor tics. Obviously, these assumptions were challenged by the negative results of the linkage studies. In addition, there is still debate about the exact nature and range of the putative TS phenotype. According to some authors, this may include forms of OCD [65] and attention deficit/hyperactivity disorder (ADHD) [66].

Meanwhile, new strategies have been enlisted in the search for the genes involved in TS, including the investigation of a number of candidate genes and regions. Candidate genes included the dopamine [67] and adrenergic [68] receptor genes, the dopamine [69] and serotonin transporter [70] genes, the catechol-o-methyltransferase [71, 72] gene and the human leukocyte antigen locus [73]. To date the candidate gene studies have been negative. Related studies have chosen candidate regions based on identified chromosomal abnormalities in individual patients; however, involvement of the candidate region could either not be confirmed [74, 75], or still awaits confirmation (a novel gene by a breakpoint in 7q31 [76]; and the contactin-associated protein 2 gene by the breakpoint at 7q35-7q36 [77]). A recent study described a TS patient with a 18q21-q22 inversion, whereby the rearrangement was fine-mapped to within 1 Mb of a 7;18 translocation (breakpoint at 18q22) present in a previously independently described TS pedigree [78] in which that translocation cosegregated with TS and related problems in that individual's family. Interestingly, fine-mapping in the recent case report iden-

tified no structurally disrupted transcripts, but instead found evidence for epigenetic abnormalities. These consisted of functional dysregulations of one or more genes in the region, in the form of a significant increase in replication asynchrony in the patient compared with controls, with the inverted chromosome showing delayed replication timing across at least a 500-kb interval [79]. This finding makes the 18q22 region an interesting candidate region and moreover points to a novel mechanism for neuropsychiatric pathogenesis, resulting from balanced autosomal gene rearrangements. The involvement of such a previously unsuspected mechanism may explain some of the difficulty in defining the genetic transmission of TS.

As a third genetic strategy, a number of nonparametric full genome scans have been carried out, using either affected sib-pairs [80], multigenerational families [81], or a case control design in an isolated Afrikaner population [82, 83]. Although some genome regions have been implicated by these studies, only the possible involvement of the 11q23 region [82, 83] has been confirmed in an independent study that involved a large French Canadian family [84]. This makes the 11q23 region probably the most interesting candidate genome area at present. A recent genome scan [85] used a more homogeneous subgroup of patients, with selection based on the presence of hoarding obsessions and compulsions, and found evidence that loci on 4q, 5q, and 17q might be associated with this TS subtype. Only the 4q locus was near a region of potential involvement identified in the previously conducted sib-pair genome scan of unselected TS patients [80]. In conclusion, while the concept of one single major TS gene now appears untenable, considerable progress has been made in the search for the genetic background of TS. Although a number of candidate regions have been identified, most of these await confirmation. Moreover, the regions of interest will still need to be fine-mapped before anything specific can be said about TS genetics at a gene level.

Notwithstanding the clear involvement of genetic factors in TS, the non-100% concordance rates for TS in monozygotic twins [57] also point to the involvement of nongenetic elements. Indeed, a number of environmental factors have been identified. These include adverse prenatal events, as evidenced by the lower birth weight in the more severely affected co-twin of monozygotic twin pairs with TS [86], and a reported association of maternal stress and severe nausea and vomiting during pregnancy with later tic severity in the offspring [87]. Stressful life events have also been linked to fluctuations in tic severity to some extent [88]. Finally, there has been quite some interest recently in the possible adverse consequences of certain infections, both with respect to tic induction and tic exacerbations. We will review this possible relationship in the following sections.

Possible role of infections in tic disorders

In the mid-1990s, several case studies entered the literature in which children were described who suddenly demonstrated severe forms of tics and obsessive-compulsive symptoms, which the authors linked to signs and symptoms of streptococcal infections [89–91]. Confronted with a failure of conventional treatment approaches, authors described the successful application of immune-based treatments in some of these cases, consisting of therapeutic plasma exchange [89–91], intravenously administered immunoglobulins [91–93] or simple use of antibiotics [91] to treat the infectious process. Such treatment modalities had not been previously employed in child psychiatry. In some cases, streptococcal reinfections were associated with the reinduction of neuropsychiatric symptoms [94]. Also, there was the notion that patients with Sydenham's chorea, which has a well-established link to group A streptococcal infections, often show behavioral symptoms, including obsessions, compulsions, and emotional lability [95]. Finally, a study had suggested the presence of autoantibodies reacting with brain tissue in patients with tics and/or OCD [96]. All in all, these observations led researchers at the National Institute of Mental Health to formulate clinical criteria for a putative subgroup of children with OCD or TS in whom symptom exacerbations were abrupt, dramatic, and temporally related to group A β-hemolytic streptococcal infections. The subgroup was designated by the euphonious acronym PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections) [94, 97]. PANDAS inclusion criteria were outlined that require the presence of OCD and/or tic disorder, prepubertal symptom onset, sudden onset or episodic course of symptoms, temporal association between streptococcal infections and neuropsychiatric symptom exacerbations, and associated neurological abnormalities. Though PANDAS-criteria require prepubertal symptom onset, cases with adult-onset symptoms that otherwise meet PANDAS criteria have been described [98, 99].

The concept of PANDAS strongly centers on Sydenham's chorea as a putative disease model, including the suggested pathogenic role of autoantibodies that cross-react with brain antigens as a hypothesized consequence of structural homology with streptococcal antigens [100]. Introduction of the concept of PANDAS has certainly done much to stimulate research and clinical interest in the potential relevance of immune factors in tic and related disorders. Concerns regarding the validity of PANDAS have been raised, however [101–104]. These include criticism about the vagueness [103, 104] of some of the criteria for PANDAS. For example, when should an exacerbation be considered abrupt? Or what time frame exactly constitutes a temporal relationship between group

A β-hemolytic streptococcal infections and symptom exacerbations? Also, concerns regarding diagnostic criteria of a streptococcal infection have been raised [101, 102]. Should a positive throat swab, without raised antistreptoccal antibody levels or symptoms suggestive of pharyngitis [105], really be considered a streptococcal infection? As an example, in a recent study, investigators claimed to have prospectively identified a number of PANDAS cases, without, however, having obtained serological evidence in the majority of putative cases [106].

In addition to the questions regarding criteria, we have three more fundamental concerns regarding the concept of PANDAS. First, in our opinion, it is far too early to call tic disorders and related disorders 'autoimmune', even when and if there is an established association with infections. As will be discussed in a later section, proving the involvement of autoimmunity in a neuropsychiatric disorder is a formidable challenge and requires much more than showing a connection with infection. Second, studies on PANDAS bear the very real risk of circular reasoning: what you include is what you find. In our opinion, research that attempts to define the extent of immune involvement in neuropsychiatric disorders should preclude the a priori selection of cases that by definition demonstrate a temporal relationship with streptococcal infections. Moreover, in a previous review [103], we pointed to the fact that, so far, no laboratory markers for immune dysregulation have been identified in PANDAS cases that have not also been described in unselected tic disorder patients. Therefore, we strongly argue for the use of unselected tic disorder patients in future studies on the extent of involvement of immune factors in tic disorders. This is not to reject the possibility that careful longitudinal studies of extreme phenotypes (e.g. those patients with the most elevated antibody titers, or those with the most marked exacerbations) might also provide a useful approach.

A third concern is that the required association with streptococcal infections in PANDAS seriously hampers unbiased investigation of other possibly involved infections in tic disorders. As an example, Allen [91] described case studies associated with viral infections. In addition, two TS cases associated with mycoplasma infections have recently been described [107]. Also, in a 6-month longitudinal study with unselected tic disorder patients, our group recently identified a highly significant association between the occurrence of a common cold and a subsequent exacerbation in tic severity in pediatric patients 4 weeks later, after symptoms of the cold had long disappeared [108]. Previously, Cardona [109] had reported a more frequent history of upper respiratory tract infections in tic disorder patients than in healthy controls subjects. Also of interest is a recent study that pointed to the importance of common colds at the time of onset of OCD and tic symptoms [110]. Thus, infections other than streptococcal infections may well be involved in tic disorders; these may include relatively common viral infections.

It is remarkable that four studies that did not preselect tic disorder according to PANDAS criteria probably found the best available evidence for an association of tic disorders with streptococcal infections [109, 111–113], even when the exact nature of this possible association remains unclear. In essence, these studies reported markedly increased serum levels of antistreptococcal antibodies in a cross-sectional single time point design. Interestingly, Cardona [109] found that levels of antistreptolysin O correlated with severity of the tics, whereas the recent study of Church and co-workers [113] identified an intriguing association between raised antistreptolysin O titers and presence of antibasal ganglia antibodies, as assessed by Western blotting and indirect immunofluorescence, in unselected TS subjects. The cross-sectional design makes these findings extremely hard to interpret, especially since antibody levels in these subjects were not assessed at the time of the first appearance of their tics, nor at a time of symptom exacerbation, but rather at an arbitrary point in time. Are patients with tics more likely to encounter streptococcal infections? Or does their immune system differently respond to streptococci, which may include a more prolonged humoral response? We really need longitudinal data to answer these and other questions. In contrast, several US studies failed to find increased single time point levels of antistreptococcal antibodies in tic disorder subjects [114–117]. Thus, even though some data may support an association between streptococcal infections and tic disorders, at present the association does not appear to be universally present, but may be confined to certain geographical areas. The potential importance of the topic lies partially in the possible relevance to treatment: the use of antibiotics to treat the underlying infections has received limited attention so far [105], but is certainly a topic that deserves further consideration.

In conclusion, some evidence is available about a possible association of streptococcal infections with tic disorders. Little can be said, however, about the nature of this association. Moreover, there is also some indication about the possible involvement of nonstreptococcal infections, including common viral infections, in exacerbations of tic disorders. With much interest we await the outcome of the ongoing longitudinal studies on this topic.

B lymphocyte surface marker D8/17

Besides a possible association of tic disorders with infections, a number of laboratory findings have been reported in tic disorders that may support the involvement of immune dysregulation. We will first review a line of re-

search which focuses on overexpression of a B lymphocyte surface marker, designated D8/17, a putative marker of susceptibility to rheumatic fever, and then summarize the findings regarding assessment of autoantibodies against neuronal tissue The monoclonal antibody against the D8/17-epitope is a mouse monoclonal immunoglobulin M (IgM) antibody that was originally prepared from fusions of spleen cells from mice that had repeatedly been immunized with isolated human B lymphocytes obtained from rheumatic fever or rheumatic heart disease patients [118]. D8/17-specific monoclonal antibody has been reported to bind with a small percentage of B lymphocytes in normal controls (averaging 5–7%), but in rheumatic fever the percentage of D8/17 positive B lymphocytes was found to be much higher (33.5% on average) [118]. It was proposed that an individual could be classified as D8/17 positive when the percentage of D8/17 positive B lymphocytes exceeded the mean + 1 SD of that of healthy controls (that is, 12%). An individual's D8/17 positivity has been reported to be a susceptibility marker for rheumatic fever, a well-known complication of infections with group A β hemolytic streptococci, with 60–100% of rheumatic fever subjects reported to be D8/17 positive [119].

In 1997, the first two reports on D8/17 in tic disorders appeared in the literature [97, 120]. Results of these studies were quite remarkable: when subjects were categorized as either D8/17 positive or D8/17 negative according to the previously established cut-off of more than 12% D8/17 positive B lymphocytes, D8/17 positivity appeared almost diagnostic for the presence of a tic disorder or OCD. In one study [120], 100% of patients (either having childhood-onset OCD or TS) appeared to be D8/17 positive versus less than 5% of healthy controls, whereas the other study [97] reported 85% of patients fulfilling PANDAS criteria to be D8/17 positive versus 17% of healthy controls. Subsequently, an association of D8/17 positivity was also reported with other psychiatric disorders, including autistic disorder [121], trichotillomania [122], and anorexia nervosa [123].

Although these D8/17 findings are intriguing, the method with which they were obtained has serious flaws. In all studies mentioned so far, D8/17 expression on B cells had been assessed by indirect immunofluorescence, whereby individual B cells were visually categorized as either D8/17 positive or D8/17 negative and counted manually by fluorescence microscopy. Three studies have used the more objective method of flow cytometry [124–126], and also found group differences between patients with a tic disorder and/or OCD and healthy controls. However, our group made use of a control IgM monoclonal antibody in addition to the antibody directed against the D8/17 epitope [125]. For this purpose, we used MOC32, an IgM monoclonal antibody that is directed against a neuroendocrine antigen of epithelial origin of small cell lung cancer cells. Upon reexamination of our data, it now appears likely that we did not detect D8/17 overexpression on B cells in tic disorder patients compared with healthy controls, but, rather, increased expression of receptors for the constant parts of IgM molecules (Fc-μ) on B cells. Thus, this appears to suggest that tic disorder patients do not express a specific susceptibility marker for experiencing autoimmune sequelae in the aftermath of streptococcal infections. Instead, the evidence may be indicative of a generalized increased immune activity.

Whatever is measured when assessing D8/17 B cell overexpression, we and other centers encountered major reproducibility problems in subsequent studies, which often were not published. Over the course of months the D8/17-specific antibody appeared to gradually lose its patient-control discriminating abilities [unpublished observations from our laboratory]. In addition, there appeared to be major differences between different antibody batches, an experience we share with others in the field [127]. At present, the molecular nature of the D8/17 epitope is unknown. Many centers have stopped using this antibody, given the failure to replicate group differences [128]. Finally, a recently published study failed to find an association between D8/17 positivity and the presence of tics or OCD in a community sample [129]. Thus, a line of research that seemed quite promising at the outset now appears to be floundering due to lack of progress in characterizing the presumed susceptibility marker. It is possible that previous positive reports were due to an unspecific increase of the number of Fc-μ receptors on B cells, a possibility that certainly deserves further study.

Antineuronal autoantibodies

The presence of autoantibodies reacting with parts of the brain that are thought to be involved in tic disorders is potentially a strong line of evidence in favor of the autoimmune hypothesis of tic disorders. In a previous review, we summarized the work carried out in this area [103]. In short, two studies assessed autoantibody binding to human caudate tissue with an indirect immunofluorescence technique in patients with tics and/or OCD [96, 120], as previously applied in patients with Sydenham's chorea [130]. Results in both studies were similar: positive staining was reported in 44–50% of tic disorder patients versus 21–24% of healthy controls. Subsequent studies using enzyme-linked immunosorbent assay (ELISA) techniques against either an immortalized neuronal cell line [131, 132], human basal ganglia [115], or rat brain [114] in general confirmed the increased levels of serum antineuronal antibodies in TS patients.

Some support for the direct involvement of antineuronal autoantibodies in the disease process stems from two different research findings. First, intravenously adminis-

tered immunoglobulins and therapeutic plasma exchange were reported to be highly effective treatments in cases fulfilling PANDAS criteria [133]. These treatment modalities are thought to block or remove the antineuronal autoantibodies, respectively. As yet, this finding still awaits confirmation. A second pillar possibly supporting a pathogenic role of antineuronal antibodies is formed by two studies in which animal models were developed to study whether serum or purified IgG from patients with TS can induce tic-like behavior in rats [134, 135]. In these studies, serum or IgG was microinfused through cannulas placed in regions of the neostriatum known to induce stereotypies, after which the rats were observed for development of movements or utterances. Hallett and co-workers [134] infused dilute serum from five TS patients, with high antibody titers against human neuroblastoma, bilaterally into the ventral striatal region of the rat. Results showed a significant increase in tic-like behaviors (e. g. licks and forepaw shakes) and episodic utterances in the TS group, which was not observed when sera from healthy controls were microinfused. Taylor and co-workers [135] infused serum from twelve TS patients, with high antibody titers against rat striatum, bilaterally into a different brain area, the ventrolateral striatal region. Results showed a significant increase of high titer-induced oral stereotypies over a 5 day period of observation. These intriguing results were not confirmed in a recent study in which Loiselle and co-workers microinfused serum from five TS children, with high antibody titers against human postmortem putamen, bilaterally into the ventral and ventrolateral striatum. In this study, no rat was reported to develop any audible abnormality, and there was no significant increase in stereotypic behaviors [104]. At our center, we also infused TS sera into rat brains at the same coordinates used in the Hallett and Taylor protocols, but did not identify any differences in tic-like behavior compared with rats that had been microinfused with sera from healthy controls [unpublished results]. We have no explanation for these conflicting results across different centers. Future studies might profit from across-center sharing of reference sera that had been previously demonstrated to induce tics.

It should be noted that as yet, no single neuronal antigenic structure has been identified as target for the putative antineuronal antibodies. Only a limited number of studies have aimed to identify separate neuronal antigens, by using Western blot techniques. Most of these studies detected candidate antigenic structures, derived from either brain tissue, or a neuroblastoma cell line, with an apparent molecular weight of 60 and/or 83 kDa [113 , 115, 132, 136]. In another Western blot study, our group recently detected, in line with existing studies, more frequent seroreactivity in tic disorder patients against a 60-kDa protein band from a neuronal cell line, compared with healthy controls, patients with autistic disorder, and patients with OCD [137]. Subsequent sequence analysis identified this 60-kDa band as the human 60-kDa heat shock protein. This protein is by no means confined to neuronal tissue; on the contrary, the human 60-kDa heat shock protein is considered to be ubiquitous [138].

Although involvement of specific neuronal antigens cannot be ruled out, the results of our study indicate that autoantibody binding to tissue of neuronal origin does not necessarily have to be confined to exclusively neuronal epitopes. This may well explain the findings of antineuronal antibodies in sera of healthy controls, as reported in earlier studies [96,120]. Though we could not directly link the presence of autoantibodies to the pathogenesis of tic disorders, our findings are still likely to support the involvement of immune factors in tic disorders. Inappropriate reactivity to heat shock proteins in humans may be understood given the high degree of antigenic homology between microbial and human hsp60, which may lead to harmful cross-reactivity with human structures [139]. It should be noted that antibodies against the human 60-kDa heat shock protein are present in virtually all subjects [140]. However, there is well-established evidence that increased reactivity to heat shock proteins is involved in autoimmune disorders [141], including rheumatic autoimmune diseases [142, 143], severe coronary heart disease, and carotid atherosclerosis [144]. Also, increased anti-hsp60 binding may be due to frequently encountered infections. In conclusion, the assessment of serum autoantibodies has appeared to be a fruitful research area in tic disorders. However, this area is very much a work-in-progress, especially with regard to characterizing antigenic structures at a molecular level and elucidating the pathogenic relevance of the antibody-antigen interactions in animal models.

Conclusion and future directions

Considerable progress has been made over the last decade with regard to the neurobiology of TS. Convincing evidence indicates that the basal ganglia and related CSTC circuits are likely to be involved in both the tics and related behavioral abnormalities. Some intriguing, though quite preliminary, neurochemical data are available that appear to indicate differences in specific neurotransmitter systems. Much progress has also has been made in the field of genetics. While independent twin and family studies had indicated the genetic background of TS and related disorders some time ago, now a number of genetic linkage and association studies have provided the first candidate loci on the human genome.

Apart from this, a number of nongenetic factors have been implicated in the pathogenesis and pathophysiology of TS, most notably adverse perinatal events and infections. Most research in this latter area has used

Sydenham's chorea as a medical model and, thus, has largely focused on the role of streptococcal infections and assessment of cross-reacting antibodies against human brain regions. Evidence for the relevance of this model for TS is still scarce, however, and is entirely based on cross-sectional studies. However, nonspecific immune activation may play a more profound role. This hypothesis is based on our findings of possibly increased receptors for the Fc-fragment of IgM on B lymphocytes, the notion of a temporal association of common viral upper respiratory infections with exacerbations of tic severity, and increased anti-hsp60 autoantibody binding in tic disorders. These findings all point to a rather general activation of the immune system that appears to be associated with tic disorders. How these alterations relate to the symptoms of TS remains unclear, but likely involves an interaction with genetic vulnerability. Thus, even though the precise mechanism is largely unknown, at present, the available evidence does indeed seem to suggest that immune factors matter in at least some individuals with tic disorders. Ongoing large-scale longitudinal studies will have to provide definite answers to this intriguing topic.

Several lines of evidence suggest that TS is likely to be a heterogeneous disorder, meaning that different pathways may lead to the disorder. Thus, clinically relevant subgroups may emerge. For example, neuroimaging studies suggest that adults who continue to demonstrate tics may have unique neuroimaging findings which are often opposite from what has been found in pediatric patients. Also, neurotransmitter abnormalities may give clues for subgroups, in which a certain neurotransmitter system may or may not be involved. To illustrate this, dopamine antagonists do not appear to have effect on tics in a significant minority of patients. Similarly, autoimmunity may be involved in only a subgroup of patients. Future genetic linkage and association studies may give better results when homogeneous subgroups are used, based on either clinical features or biological markers. Also, combining different research tools, e.g. neuroimaging with immune factors, may prove fruitful. Giedd and co-workers [90] described an interesting case study in which enlargement of basal ganglia volumes decreased dramatically in response to therapeutic plasma exchange. Peterson and co-workers [116] studied the relationships between antistreptococcal antibody titers and basal ganglia volumes in a cross-sectional design. Interestingly, higher antibody titers in subjects with ADHD or OCD were associated with larger volumes of the putamen and globus pallidus nuclei; surprisingly, higher titers were not seen in tic disorder patients. In another example of combining research approaches, the National Institute of Mental Health group assessed first-degree relatives of 54 children fulfilling criteria for PANDAS for the presence of a tic disorder [145]. Results were remarkably similar to those of family studies using non-PANDAS tic disorder probands. Integrating neuroimaging, neurochemistry, genetics, and neuroimmunology may prove to be an especially powerful approach. Ultimately, however, identifying the involvement of major genes will allow for more definite studies of gene-environment interactions, both through study of animal models and of high-risk children known to be affected by such genes.

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