Antibasal ganglia antibodies and their relevance to movement disorders

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Purpose of review

Recently, autoaggressive immunological responses were included among the causative agents of basal ganglia dysfunction. Autoaggressive immune-mediated illnesses secondary to group A beta-haemolytic streptococcal infections present with motor and psychiatric symptoms, due to basal ganglia involvement. These disorders have been associated with serum antineuronal antibodies, relatively specific to human basal ganglia tissue. This review summarizes the most recent studies concerning antibasal ganglia antibodies, focusing on the associated phenotypes and the hypotheses concerning their pathogenicity.

Recent findings

The spectrum of post-streptococcal neuropsychiatric disorders associated with antibasal ganglia antibodies seems broader than previously recognized. Other than chorea, tics and obsessive–compulsive disorder, which constituted the bulk of previously described disorders associated with antibasal ganglia antibodies, post-streptococcal neuropsychiatric disturbances include a wider range of motor and behavioural abnormalities, in keeping with the multifunctional role of the basal ganglia. An encephalitis lethargica-like illness following streptococcal infection was reported, and unusual adult-onset movement disorders associated with antibasal ganglia antibodies were documented. Moreover, investigators provided preliminary evidence for a pathogenic role of autoantibodies in Sydenham's chorea, the prototypic post-streptococcal neuropsychiatric disorder.

Summary

Antibasal ganglia antibodies are relatively specific in identifying post-streptococcal neuropsychiatric disorders, which constitute a wider spectrum of movement disorders than previously recognized. Although their sensitivity in diagnosing Sydenham's chorea seems excellent, it is not yet possible to extrapolate this sensitivity to all the recently identified post-streptococcal neuropsychiatric disorders. The antigens targeted by these autoantibodies and their pathogenic importance are currently under investigation. Preliminary evidence suggests that antibasal ganglia antibodies may be pathogenic.

Keywords

anti-basal ganglia antibodies, group A beta-hemolytic streptococcal infections, PANDAS, encephalitis lethargica

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Abbreviations

ABGA	autoantibody reacting against basal ganglia antigens
ADEM	acute disseminated encephalomyelitis
ADHD	attention deficit/hyperactivity disorder
ARF	acute rheumatic fever
CNS	central nervous system
CSF	cerebrospinal fluid
EL	encephalitis lethargica
GABHS	group A beta-haemolytic streptococcal infection
OCD	obsessive–compulsive disorder
PANDAS	paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection
PSND	post-streptococcal neuropsychiatric disorder
SC	Sydenham's chorea
TS	Tourette's syndrome

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Introduction

Over the past 15 years, there has been a growing interest in autoaggressive immune-mediated disorders of the basal ganglia. Several reports have suggested the presence of autoantibodies reacting against basal ganglia antigens (ABGAs) in the serum of patients presenting with different movement disorders [1–4]. An autoaggressive immune-mediated insult to this brain region has been proposed to occur as a direct result of an infectious [5] or a paraneoplastic process [6,7]. It may also occur in the context of a systemic connective tissue disease involving the central nervous system (CNS) [8].

Classically, ABGAs have been described in the context of a neuropsychiatric syndrome occurring in association with group A beta-haemolytic streptococcal infections (GABHSs). Based on the model of acute rheumatic fever (ARF), the prototypic post-streptococcal immune-mediated autoaggressive disorder, molecular mimicry between antigens on GABHS and human neural tissue is the favoured immunological mechanism underlying the pathogenesis of these disorders [9]. The neuropsychiatric manifestation of ARF, Sydenham's chorea (SC), was the illness in which ABGAs were first demonstrated [10]. Whether these ABGAs are pathogenic or not or simply represent diagnostic markers has yet to be resolved. The more recently described syndrome of paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) has also implicated post-infectious autoimmunity in a subset of patients with childhood onset tics and obsessive–compulsive disorder (OCD) [11]. PANDAS is also associated with the presence of ABGAs [1]. The clinical

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spectrum of SC and PANDAS is relatively narrow, and it is not surprising therefore, considering the role of the basal ganglia in the control of movement and emotions, that the clinical spectrum of ABGA-related disorders is much broader [12]. This review will focus on the clinical spectrum of movement disorders associated with ABGAs.

Sydenham's chorea

Patients with SC produce antibodies that cross-react between the rheumatogenic strains of streptococci and human basal ganglia [10,13]. In order to assess the accuracy in discriminating SC of different laboratory methods that detect ABGAs, Church *et al.* [4] compared immunofluorescence microscopy, enzyme-linked immunosorbent assay and Western immunoblotting techniques. Immunofluorescence microscopy showed antibody binding to tracts of neurons in the caudate head. However, its specificity was limited, because of the subjective nature of the technique. Although an ABGA enzyme-linked immunosorbent assay has the advantage of a relatively high throughput compared with immunofluorescence microscopy and Western blot, its specificity was lower. Conversely, Western blot allows the identification of the molecular weight of the antigens involved in antibody binding and had the highest diagnostic specificity. On Western blot, ABGAs were detected in 100% of acute SC patients and in 69% of convalescent SC, compared with significantly lower binding in rheumatic fever without SC (12%) or healthy paediatric controls (0%). Reactivity to basal ganglia antigens of 40 000, 45 000, and 60 000 M_r was commonly seen in both acute and persistent cases of SC. Despite some methodological controversy regarding the Western blot assay [14], this method seems to be the most suitable assay at present to detect ABGAs. Interestingly, ABGAs have recently been described in a 19-year-old woman with chorea induced by the oral contraceptive pill [15•], a condition classically considered to represent a relapse of SC [16].

From paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection to post-streptococcal neuropsychiatric disorders

PANDAS represents a relatively new paediatric syndrome, characterized by acute onset of OCD or tic disorder (meeting Diagnostic and Statistical Manual of Mental Disorders version IV criteria) after GABHSs, with a clear temporal relationship between the GABHSs and the exacerbations of neuropsychiatric symptoms [11]. It has been postulated that PANDAS and SC share a common pathogenesis [17,18]. Neuropsychiatric manifestations (mainly OCD) are common in SC, and the two syndromes may simply represent two variants of a single disorder [2]. Interestingly, the same psychiatric symptoms observed in PANDAS have also been documented in patients with rheumatic fever, but without SC [19]. Moreover, both SC and PANDAS appear to respond to immunomodulatory therapy [20,21,*22*•]. Several case reports have described a range of childhood-onset movement disorders, neither fulfilling the diagnostic criteria for SC nor for PANDAS, as the sequelae to a preceding streptococcal infection. Two children with acute infantile bilateral striatal necrosis after GABHS pharyngitis had antibodies reactive against basal ganglia constituents of 40 000 M_r, and immunohistochemistry showing selective reactivity to large striatal neurons [23]. A case of paroxysmal dystonic choreoathetosis occurring after GABHS pharyngitis was reported, in association with ABGA binding to 80 000 and 95 000 M_r antigens [24]. The acute onset of generalized and segmental myoclonus associated with recent streptococcal infection has also been reported [25,26], but ABGAs were not looked for in those patients.

Dale *et al.* [27] conducted a prospective study on children from a tertiary care setting, who presented with a movement disorder that followed serologically or culture-confirmed streptococcal pharyngitis. Their clinical details are summarized in Table 1. All the children presenting with chorea or tics fulfilled the criteria for SC or PANDAS, respectively, but the range of other symptoms and signs observed in the cohort indicates that post-streptococcal neuropsychiatric disorders (PSNDs) have a broader phenotype than SC or PANDAS. In this group of patients, the presence of ABGAs discriminated between children with PSNDs with a sensitivity of 93%, a specificity of 97%, a positive and negative predictive value of 97% and 91%, respectively [28]. ABGAs performed similarly well in the SC, PANDAS and other movement disorder subgroups. Importantly, the same three dominant basal ganglia antigens of 40 000, 45 000 and 60 000 M_r were the discriminators. The authors concludes that ABGAs could be used as a marker for movement disorders related to GABHSs (Table 2).

Encephalitis lethargica and post-streptococcal neuropsychiatric disorders

Parkinsonism (bradykinesia and rigidity) is an uncommon manifestation of PSND. Ben-Pazi *et al.* [43] documented an akinetic-rigid syndrome in a 10-year-old girl during an episode of SC, associated with an elevated antistreptolysin-O titre and ABGA binding to a 60 000 M_r antigen. A recent study proposed that encephalitis lethargica (EL) or an EL-like illness should also be included in the spectrum of PSND [42••]. EL, first described by von Economo in 1916, is a CNS disorder manifesting with sleep disturbance, lethargy,

Table 1. The extended spectrum of post-streptococcal neuropsychiatric disorders

Movement disorders		Psychiatric symptoms	
Chorea	20 (50%)	Aggressive, oppositional or disruptive behaviour	14 (35%)
Vocal tics	17 (42.5%)	Emotional lability	13 (32.5%)
Motor tics	16 (40%)	Anxiety	11 (27.5%)
Dystonia	5 (12.5%)	Obsessive–compulsive behaviour	9 (22.5%)
Tremor	3 (7.5%)	Sleep disorders	9 (22.5%)
Stereotypies	2 (5%)	Depression	7 (17.5%)
Opsoclonus	2 (5%)	Attention deficit	7 (17.5%)
Myoclonus	1 (2.5%)	Echolalia	4 (10%)
Paroxysmal dystonic choreoathetosis	1 (2.5%)	Visual hallucinations	2 (5%)
		Social disinterest	2 (5%)

Modified from Dale ***et al.*** [27], with permission.

parkinsonism and neuropsychiatric sequelae, occurring both in an epidemic and sporadic form [44]. Despite the overlap between the 1918 influenza and the 1916–1927 EL pandemics, recent analyses of archived EL brain specimens make a causal link unlikely [45]. Dale *et al.* [42••] described 20 patients (two of whom were adults) with an EL-like syndrome (Fig. 1), characterized mainly by an acute or subacute onset and a variable course. Fifty-five per cent of these were preceded by pharyngitis or tonsillitis. Evidence for viral encephalitis was excluded, and the cerebrospinal fluid (CSF) showed elevated total protein and oligoclonal IgG bands. The latter was caused either by an intrathecal or systemic pattern of oligoclonal IgG production. Magnetic resonance imaging showed inflammatory changes in the basal ganglia and midbrain tegmentum in 40% of patients, which resolved during convalescence. Histopathology in one case revealed perivascular cuffing of B and T lymphocytes, predominantly in the basal ganglia, reactive astrocytes and macrophages, showing remarkable similarity to the pathology of SC [46]. Two-thirds of the patients had elevated antistreptolysin-O titres during the acute phase. Most importantly, Western blot showed ABGAs in 95% of these patients, predominantly reactive to 40 000, 45 000, 60 000 and 98 000 M_r antigens. Immunohistochemistry revealed a similar antibody binding pattern to that seen in SC (cytoplasm of axons and somata, within tracts of neurons in the caudate, putamen and substantia nigra). These findings therefore support the inclusion of an EL-like syndrome within the group of immune-mediated neuropsychiatric sequelae of streptococcal infections.

Post-streptococcal acute disseminated encephalomyelitis

Acute disseminated encephalomyelitis (ADEM) is a post-infectious autoimmune CNS disorder mainly affecting the white matter, but in which cortical or subcortical gray matter lesions occur in almost 30% of patients. Several viruses, bacteria and vaccines have been implicated in its aetiology. Unlike other ADEM subtypes, post-streptococcal ADEM manifests with a dystonic extrapyramidal syndrome in 50% of cases, and a behavioural syndrome in 70% of cases [5]. In 80% of cases, there are inflammatory changes in the basal ganglia, and in 90% ABGA binding (mainly to 60 000, 67 000 and 80 000 M_r antigens) has been reported [5]. The clinical presentation of post-streptococcal ADEM and the EL-like cases described above are very similar, and probably represent the same disease.

Tourette's syndrome

Based on the PANDAS hypothesis, it has been proposed that GABHSs may play a role in a subset of patients with Tourette's syndrome (TS) [47]. Oral tic-like stereotypies were induced in rats, after bilateral infusion in the ventrolateral striatum of sera from patients with TS and high levels of antineural antibodies [48,49]. Another group, however, failed to reproduce these results, using sera of patients with TS and PANDAS [50]. Several cross-sectional studies have reported increased antistreptolysin-O and antiDNAse B antibody titres in children and adults with TS, compared with age-matched healthy and neurological controls [33,35,37•]. A recent paediatric series [39] did not confirm this finding, but used only a single point in time to look for evidence of recent streptococcal infection. Immunoreactivity to human striatum has been repeatedly documented from the sera of TS patients. The first reports focused attention upon a 60 000 and an 83 000 M_r antigen [3,36]. More recently, Church *et al.* [37•] described ABGA reactivity against the same antigens involved in other PSNDs (40 000, 45 000 and 60 000 M_r) in 20% of 56 children and 27% of 44 adults with TS. This was highly significant, as ABGAs were rare in healthy and other neurological controls. Interestingly, raised antistreptolysin-O titres were more frequent in ABGA-positive than in ABGA-negative patients, further supporting the link between streptococcal infection and ABGAs. No significant clinical differences among TS patients, according to their ABGA status, were observed. The same results were reproduced by other groups: in particular, Hoekstra *et al.* [40]

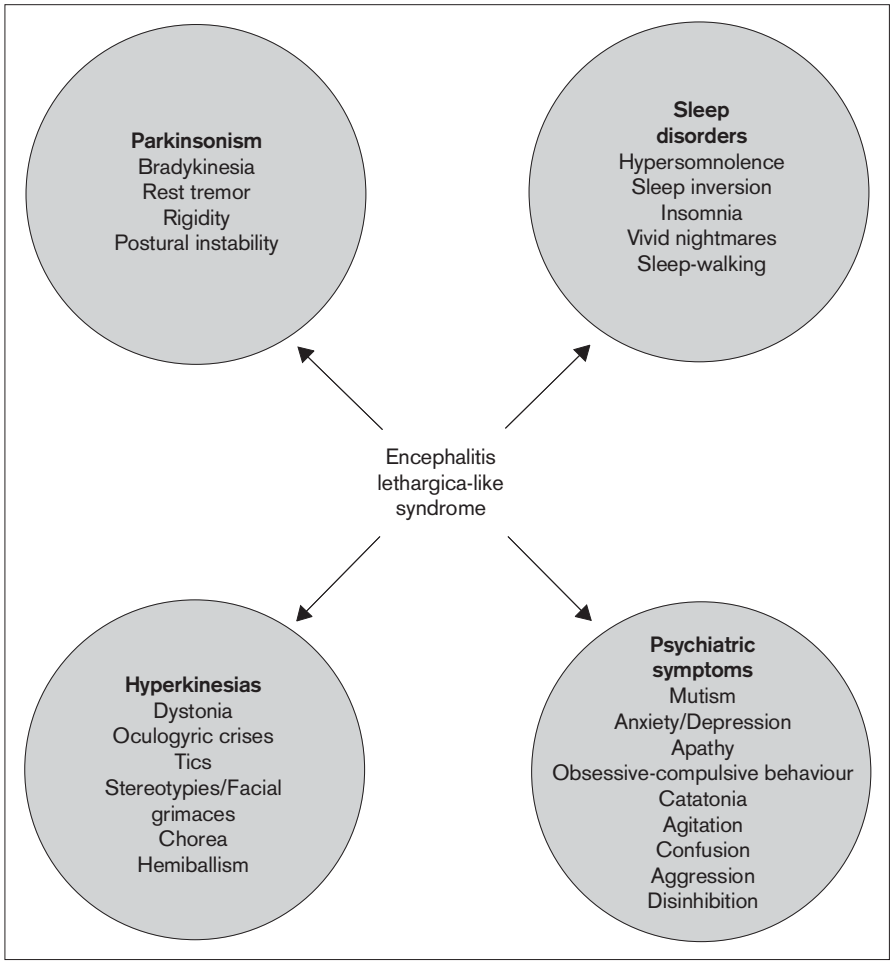
Table 2. Cross-sectional case–control studies investigating the presence of anti-streptococcal antibodies and autoantibodies reacting against basal ganglia antigens in patients with neuropsychiatric disorders included in the 'post-streptococcal' spectrum

Authors	Phenotype	Patients/controls (*N*)	Antistreptococcal antibodies	ABGA
Husby G *et al.* 1976 [10]	SC	30/55	Not reported	$P<0.005$[c]
Kiessling *et al.* 1993 [1]	Movement disorders (tics/chorea)	45/38[b]	ASO and/or anti-DNAse B, ns	RR 2.3, $P=0.001$[c]
Swedo *et al.* 1993 [2]	SC	11/18	ASO, mean of patients: 680 Todd units (normal values $\leqslant$480)	RR 5.26, $P=0.04$[c]
Murphy *et al.* 1997 [29]	OCD	31[a]/21	ASO, ns; anti-DNAse B, ns	ns[c]
	TS		ASO, ns; anti-DNAse B, ns	
Kotby *et al.* 1998 [30]	SC	40/40	ASO, >480 Todd units in 30% of patients (mean 600)	$P<0.01$[c] only in patients with active chorea
Singer *et al.* 1998 [3]	TS	41/39	ASO, ns; anti-DNAse B, ns	$P=0.006$[d]; higher frequency among patients[e]
Singer *et al.* 1999 [31]	TS	41/39	Not done	$P=0.012$[d]; similar frequency[e]
Muller *et al.* 2000 [32]	TS	36[a]/52[b]	ASO, $P\leqslant0.01$ in children, ns in adults; anti-DNAseB, $P\leqslant0.0005$ in children, ns in adults	Not done
Peterson *et al.* 2000 [33]	CTD	53/20	ASO, ns; anti-DNAse B, ns	Not done
	OCD	27/20	ASO, ns; anti-DNAse B, ns	Not done
	ADHD	41/20	ASO, $P=0.03$; anti-DNAse B, $P=0.03$	Not done
Dale *et al.* 2001 [5]	Post-streptococcal	10/80[b]	ASO, $P=0.002$; anti-DNAseB, $P<0.001$ (both compared with the neurol. control)	$P<0.001$[d] (compared with both groups)
	ADEM			Western blotting: sensitivity 100; specificity 92%
Muller *et al.* 2001 [34]	TS	25[a]/25	ASO, $P=0.025$; anti-DNAse B, $P<0.001$	Not done
Wendlandt *et al.* 2001 [35]	TS	20/21	Not done	$P=0.0007$ (using MANOVA and discriminant analysis)[e]
Morshed *et al.* 2001 [36]	TS	81[a]/67[b]	ASO, $P=0.007$; anti-DNAseB, ns	$P=0.006$[c]
	SC	27[a]/67[b]	ASO, $P=0.04$; anti-DNAseB, $P=0.023$	$P=0.0001$[c]
Church *et al.* 2002 [4]	SC	36/27[b]	Not done	$P<0.001$[c] (compared with both control groups) WI: sensitivity 100%; specificity 93%
Church *et al.* 2003 [37•]	TS	100[a]/190[b]	ASO, $P<0.0001$ in children, $P<0.05$ in adults	$P<0.05$[e] in children and adults
Loiselle *et al.* 2003 [38•]	TS	41/38	ASO, ns; anti-DNAse B, ns	Not done
	ADHD	20/59	ASO, $P=0.04$; anti-DNAse B, ns	Not done
	OCD	8/71	ASO, ns; anti-DNAse B, ns	Not done
Singer *et al.* 2003 [14]	SC	9/9	Not done	$P<0.0001$ (using MANOVA and discriminant analysis)[e]
Dale *et al.* 2003 [39]	OCD	50/140[b]	Not done	48% patients and 4% controls were positive[e]
Hoekstra *et al.* 2003 [40]	Tics	82/83[b]	Not done	67% patients and 40–42% controls were positive
Rizzo *et al.* 2003 [41]	TS	69/73[b]	59% patients versus 19% controls had raised ASO titre	31% patients versus 12% controls had positive ABGAs[f]
Dale *et al.* 2004 [42••]	EL	20[a]/173[b]	ASO, $P<0.005$ compared with all control groups	$P<0.0001$[e]
Church *et al.* 2004 [28]	Chorea, tics, dystonia and other movement disorders	40/190[b]	ASO, $P<0.005$ compared with all control groups, except the child streptococcal group	ELISA: $P<0.001$, sensitivity 82%, specificity 79%
			Elevated titres among selection criteria	WI: sensitivity 92%, specificity 95%

ABGA, Autoantibody reacting against basal ganglia antigens; ADEM, acute disseminated encephalomyelitis; ADHD, attention deficit/hyperactivity disorder; ASO, antistreptolysin-O; EL, encephalitis lethargica; ELISA, enzyme-linked immunosorbent assay; MANOVA, multivariate analysis of variance; OCD, obsessive–compulsive disorder; SC, Sydenham's chorea; TS, Tourette's syndrome; WI, Western immunoblotting. [a]The patient group includes both children and adults. [b]Control groups include both pathological and healthy controls. [c]Detected by indirect immunofluorescence. [d]Detected by ELISA. [e]Detected by WI. [f]Method not reported.

confirmed increased seroreactivity against a 60 000 M_r antigen in a group of 82 tic disorder patients. Antibody reactivity against striatum has also been reported in psychiatric illnesses, often occurring co-morbidly with TS, such as attention deficit/hyperactivity disorder (ADHD), OCD (see below) and autism [51]. Longitudinal studies are needed to investigate this apparent overlap between TS and PSNDs further.

Figure 1. The clinical spectrum of the encephalitis lethargica-like syndrome associated with group A beta-haemolytic streptococcal infection



Obsessive–compulsive disorder

Like tics, OCD is a well recognized feature of PSNDs. Post-streptococcal autoimmunity might therefore be involved in a subset of patients with isolated OCD. Measures of cellular immune responses in individuals with non-PANDAS OCD have provided fairly inconsistent results [52,53]. Increased expression of the poorly defined surface marker D8/17 on B lymphocytes, considered a susceptibility marker in ARF [54], has been repeatedly observed in patients with OCD and tics, but the lack of methodological standardization has prevented the further assessment of this marker in this group of disorders [55]. Cross-sectional TS studies assessing antistreptococcal titres have yielded contradictory results [33,54]. Murphy *et al.* [56••] followed 25 children (average age 10 years) with OCD or tic disorder for an average period of 16.5 months, evaluating them at 6-week intervals for neuropsychiatric severity and GABHS titres. They noticed that, in children with large clinical fluctuations, there was a positive correlation between streptococcal titres and OCD severity, revealing a fluctuating PANDAS-like course of post-streptococcal OCD. Such a finding was less striking for tics, probably because of the short period of observation and the relatively older age of the children. In a cross-sectional study, another group [39] compared 50 children with OCD with 100 children with neurological disorders and 40 with recent uncomplicated streptococcal infection: 48% of the OCD patients had ABGAs to 40 000, 45 000 and 60 000 M_r antigens, compared with 4% of controls. ABGA-positive OCD patients were likely to have co-morbid tics and positive GABHS serology. ABGAs, therefore, seem to be promising markers to differentiate post-streptococcal OCD from the general population of patients with this disorder.

Attention deficit/hyperactivity disorder

The co-morbidity of ADHD has been suggested to predict the development of SC in patients with ARF, consistent with the pathogenic involvement of the basal

ganglia in ADHD [19]. Peterson *et al.* [33] showed that a Diagnostic and Statistical Manual of Mental Disorders version IV diagnosis of ADHD was significantly associated with antistreptolysin-O and antiDNAse B titres, regardless of the co-occurrence with chronic tic disorder or OCD. Waldrep [57] reported two children with episodic ADHD after GABHSs, in the absence of tics and OCD, which responded dramatically to antibiotics. Cross-sectional and longitudinal observations of ABGAs in ADHD are needed to test whether ABGAs are useful in discriminating a subset of patients with post-streptococcal ADHD.

Adult-onset movement disorders

PSNDs have been described almost exclusively in children. Nevertheless, recent case reports have documented the acute or subacute onset of movement disorders or behavioural symptoms precipitated by upper respiratory infections in adults [58–60]. Bodner *et al.* [58] reported a 25-year-old man with a sudden onset of OCD after severe antibiotic-responsive pharyngitis. He fulfilled all the working criteria for PANDAS, apart from the age of onset. ABGAs are uncommon in typical adult-onset basal ganglia disturbances [61,62]. Recently, another group assessed the frequency of ABGAs in 65 patients with adult-onset movement disorders with an unusual presentation [62]. Forty-two had ABGAs in their serum, reactive to the 40 000, 45 000 or 60 000 M_r antigens. Positive patients were more likely to be younger, and to present with an isolated fixed dystonia of a limb. Interestingly, ABGA-positive movement disorders were more frequently associated with precipitating factors, particularly recent infections, than ABGA-negative movement disorders. Other than dystonia, the group of positive patients included individuals with tics, Parkinsonism, myoclonus, chorea and ataxia.

The pathogenic role of autoantibodies reacting against basal ganglia antigens

Despite their clinical correlation with streptococcal infections, the role of ABGAs in PSNDs has not been adequately defined. According to the leading theory, ABGAs are induced by a process of molecular mimicry. The antigens, which are currently unknown, are likely to be highly conserved molecules, significantly enriched in the basal ganglia, common to both streptococci and humans. Immune-mediated cross-reactivity between GABHSs and the human brain is likely to play a central role in the pathogenesis of PSNDs. A randomized combined open-labelled plasma exchange and double-blinded placebo-controlled intravenous immunoglobulin study demonstrated both interventions to be effective in reducing tics and OCD in children with PANDAS [20]. Similarly, intravenous methyl-prednisolone followed by oral prednisone has also been reported to be effective and well tolerated, at least in the short term, in a small series of patients with SC refractory to valproic acid and neuroleptic agents [22•]. These treatment responses support the hypothesis that these disorders are immunologically mediated, but do not tell us whether ABGAs are directly causing the neuronal dysfunction that underlies these disorders, or merely represent an epiphenomenon of an ongoing immune response, presumably driven by GABHSs. Whether this immune response is predominantly cell mediated, rather than antibody mediated, awaits further study, despite preliminary findings in support of an antibody-mediated process. Church *et al.* [63] showed a cytokine pattern in the serum and CSF of patients with SC compatible with a T helper type 2 T-cell response. T helper type 2 immune responses are more likely to be associated with an autoantibody-mediated pathogenesis. The study also reported, for the first time, the presence of ABGAs in the CSF of patients with SC [63]. Kirvan *et al.* [64••] tested monoclonal antibodies derived from human hybridomas from a patient with SC for cross-reactivity between GABHSs and the brain. One of these antibodies was highly specific to the mammalian lysoganglioside GM1 and to *N*-acetyl-beta-D-glucosamine, the dominant epitope of the GABHS surface carbohydrate. Both the reactive monoclonal antibody and the sera from patients with active chorea, induced calcium/calmodulin-dependent protein kinase II activity, an enzyme involved in signal transduction mechanisms, whereas sera from convalescent patients did not. As many brain gangliosides participate in neuronal intracellular signalling and in the modulation of neurotransmitter release, the authors speculated that their findings constitute initial evidence for a direct pathogenic effect of ABGAs in patients with SC and, by inference, other PSNDs. However, the specific reactivity of ABGAs, as detected by Western blot analysis, is inconsistent with an exclusive role of antiganglioside antibodies in this group of disorders. Further evidence in favour of a pathogenic role for autoantibodies comes from a recent murine model of PSND, in which, surprisingly, GABHS-immunized mice showed the highest correlation of abnormal behaviours with serum immunoreactivity to deep cerebellar nuclei [65••].

Conclusion

ABGAs have been detected in a large number of disorders associated with basal ganglia dysfunction that are temporally related to GABHSs. The clinical spectrum of PSNDs has recently been extended to include most movement disorder phenotypes associated with basal ganglia dysfunction. This group of disorders includes encephalitic illnesses with an ADEM or EL-like onset. Together with throat culture and antistreptococcal antibodies, ABGAs are useful diagnostic markers in making a diagnosis of PSNDs. The high frequency of ABGAs in TS and OCD, in association with evidence of

recent streptococcal infection, suggests a possible pathogenic role for GABHSs in a subgroup of patients with these illnesses. Conclusive evidence from longitudinal and epidemiological studies is warranted. Despite the antigenic targets of ABGAs remaining undefined, interesting initial findings support a pathogenic relevance of these autoantibodies in PSNDs.

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