# Three cases of symptom change in Tourette's syndrome and obsessive-compulsive disorder associated with paediatric cerebral malignancies

Bradley S Peterson, Richard A Bronen, Charles C Duncan

**Abstract**

*Objective*—To correlate behaviour manifestations with tumour location in three children who had Gilles de la Tourette's syndrome (GTS), obsessive-compulsive disorder (OCD), and primary cerebral malignancies.
*Method*—Cases were ascertained from a chart review in a GTS and OCD specialty clinic. For each case the temporal progression of change in neuropsychiatric symptoms was qualitatively correlated with radiographic documentation of tumour progression.
*Results*—The change in symptom severities during tumour progression and treatment, together with prior neurobiological studies of GTS, suggest that the ventral striatum, corpus callosum, thalamus, and midbrain are potentially important neural substrates in the formation or modulation of tic symptoms. The limbic system, including the hypothalamus and cingulate, and the caudate nucleus, seem to be important in the neurobiology of OCD. All structures are neuroanatomically and functionally related to the corticostriato-thalamocortical circuitry that is thought to subserve symptom generation in both GTS and OCD.
*Conclusion*—Although the malignancies were not likely to have caused the tic and OCD symptoms in these children, the locations of these intracranial lesions provide important clues in identifying brain regions that may contribute to the determination of tic and OCD severities.

(*J Neurol Neurosurg Psychiatry* 1996;61:497–505)

Keywords: Tourette's syndrome; obsessive-compulsive disorder; neoplasms

Yale Child Study Center, New Haven, CT, USA
B S Peterson

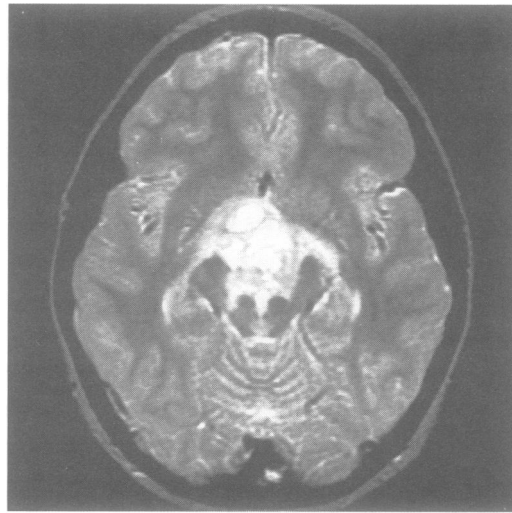Yale University School of Medicine in New Haven, CT, USA
B S Peterson
R A Bronen
C C Duncan

Correspondence to:
Dr B S Peterson, Yale Child Study Center, 230 South Frontage Road, New Haven, CT 06520, USA.

Gilles de la Tourette's syndrome (GTS) is a childhood onset movement disorder consisting of multiple motor and phonic tics that fluctuate in severity. It is thought to be aetiologically related to at least one form of obsessive-compulsive disorder (OCD),[1] a neuropsychiatric illness characterised by the experience of recurrent, intrusive, and distressing thoughts, images, and urges to action. In clinical settings GTS is also often associated with attention deficit hyperactivity disorder (ADHD).

We describe three cases of GTS and OCD associated with paediatric cerebral malignancies. In each case, GTS and OCD symptoms seemed to change during specific phases of tumour development and treatment. For each case we attempt to correlate lesion location with changes in symptomatology. These correlations may aid in identifying the neurobiological substrate of GTS related disorders. The cases were ascertained from among more than 800 that presented to our GTS/OCD specialty clinic over a period of 10 years.

## Case 1
A right handed girl at the age of 8 developed unilateral facial tics, vocal tics, and compulsive stereotypies during progression of her optic chiasm astrocytoma.

### EARLY INTRAMORBID COURSE
Her tumour was first diagnosed at the age of 18 months when she presented with accelerated linear growth. Because her growth slowed substantially during a trial of bromocriptine, the tumour was erroneously thought to be benign.

### TUMOUR DESCRIPTION
Yearly MRI showed a large tumour that seemed stable in size (fig 1A and B). The tumour involved the entire rostrocaudal extent of the hypothalamus, and extended bilaterally (right greater than left) into the thalami, inferior genu, the posterior limb of the internal capsule, ventral striatum, nucleus accumbens, septal nuclei, and the columns of the fornix. The tumour extended minimally into the posterosuperior aspect of the amygdala and did not seem to involve the hippocampus. Inferiorly it invaded the medial substantia nigra bilaterally and surrounded both red nuclei. The caudate nuclei appeared thinned due to dilatation of both lateral ventricles.

### FAMILY AND DEVELOPMENTAL HISTORY
The girl's maternal grandfather had obsessive preoccupations with orderliness, cleanliness, germs, and disease, and corresponding ordering, arranging, and cleaning compulsions that met DSMIII-R criteria for OCD,[2] but that never required treatment. No family member had a history of motor or vocal tics. Other than her large stature, this girl's early growth and development were normal until the age of 7, when she began to exhibit brief periods of unexplained aggression. Although she gained

nocturnal continence by the age of 7, nightly enuresis returned at the age of 8.

### GTS AND OCD SYMPTOMS
Shortly after she was 8 she developed frequent throat clearing and lyrical vocal tics that were soon followed by a left facial tic, a left eye-blinking tic, and non-purposeful, left sided mouth opening. She also often readjusted the glasses on her nose until they felt "just right".

### PROGRESSION
Tics increased in frequency and intensity over the next five months. At the age of 8 years and 5 months she experienced acute loss of vision, headache, vomiting, and episodic loss of consciousness. Brain CT showed obstructive hydrocephalus. She underwent a non-curative tumour resection that involved a bifrontal craniotomy, retraction of both cerebral hemispheres, section of the anterior corpus callosum, and partial tumour excision.

### POSTOPERATIVE TUMOUR DESCRIPTION
Postoperative MRI showed surgical resection and retractor injury involving the fornices bilaterally, left wall of the third ventricle, left hypothalamus, genu of left internal capsule, left caudate nucleus head, right cingulate gyrus, and mid-body of the corpus callosum (fig 1C). Histopathological analysis of the tumour disclosed a highly malignant grade II astrocytoma. Two months later she underwent

palliative radiation treatment, receiving 5400 cGY in the region of her optic chiasm.

### SYMPTOM PROGRESSION
Immediately after surgery her simple motor and vocal tics abruptly disappeared. She soon developed, however, numerous repetitive, self stimulating, and self manipulating stereotypies and compulsions. She constantly rocked back and forth and picked her nose or ears until they bled. She rubbed sand into her scalp without explanation, and she compulsively fondled her genitals in public. Other compulsions were more bizarre. She would pick her nose and then insert the mucus into her vagina or rectum. She could not offer explanations for these behaviours, other than to say she could not stop herself. She developed an obsessive preoccupation with tactile stimuli, especially with the feeling of clothes on her body and the texture of objects. She also developed a hyperphagia that produced a weight gain of more than 40 pounds in as many days. She rummaged through garbage cans for food and locks had to be put on refrigerator doors. Neuropsychological deficits documented, after surgery and before radiation therapy, a verbal IQ of 123, a performance IQ of 77, and impaired immediate and delayed recall.

### OUTCOME
Four months after surgery the girl again had a rapid decline in visual acuity and MRI documented rapid tumour enlargement. She began a course of carboplatinum and vincristine. Serial MRI documented no further growth of her tumour nearly five years after her partial resection. She has outlived all medical predictions for her life expectancy.

## Case 2
A right handed boy had had obsessive-compulsive symptoms and tics since the age of 7. He developed a left parietal anaplastic mixed glial cell malignancy.

### EARLY INTRAMORBID COURSE
This boy was intelligent and well adjusted

*Figure 2 Case 2: parietal anaplastic glial cell tumour. Sagittal T1 weighted (A), axial proton density weighted (B), and coronal proton density weighted images show the tumour to be hypointense to grey matter on T1 weighted images and hyperintense on proton density scans, with regions of signal hypointensity consistent with calcification (arrowhead). This large tumour involves the body of the corpus callosum (b), the left cingulate gyrus (c), fornix, and body and tail of the left caudate nucleus.*



A
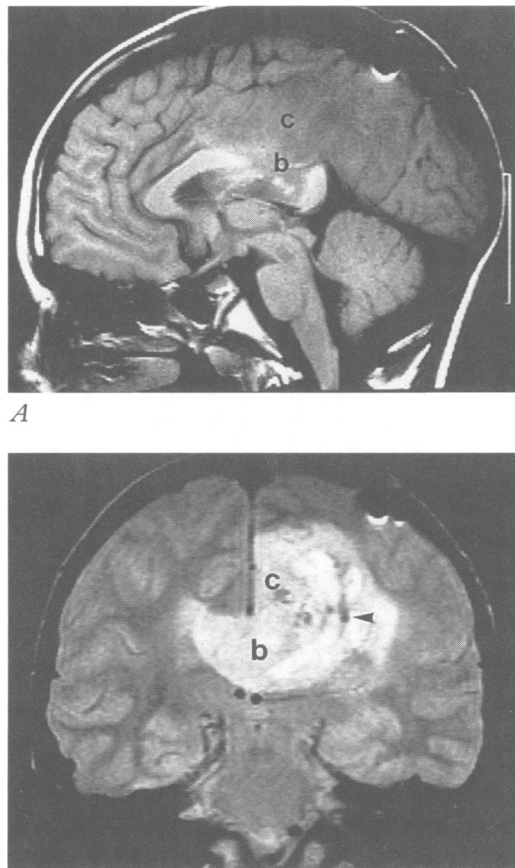


B

despite the presence of infrequent eye blinking and throat clearing tics since the age of 7, which his family regarded as a habit and for which they did not seek treatment. Although he did not meet formal criteria for OCD, he kept all of his belongings spotless and his clothing and toys neatly arranged.

FAMILY AND DEVELOPMENTAL HISTORY

A maternal uncle and cousin had chronic facial tics, but no family member had GTS or OCD. Occasional bedwetting episodes began at the age of 8, after a year of nocturnal continence. At the age of 9 he developed a left sided focal sensory seizure disorder that began with left sided facial numbness before generalising. Neurological examination was normal, but an EEG showed "Rolandic" epileptiform discharge from the right central mid-temporal region. A non-contrast head CT was normal, and a diagnosis of benign focal epilepsy was made. Phenytoin was started after several bouts of enuresis raised the possibility of nocturnal seizures.

GTS AND OCD SYMPTOMS

At the age of 11 spontaneous and darting leftward conjugate eye movements began. These were soon accompanied by a dystonic leftward head turning tic. Multiple neurological investigations were unrevealing, and the movements were diagnosed as simple motor tics. A routine follow up EEG disclosed a single right anterior mid-temporal sharp wave transient that was suggestive of an irritative process, although the anomaly was deemed to be an artifact.

Tics were infrequent initially, but three

months later increased acutely, producing scores of eye movements each minute. Covert tongue thrusting that badly eroded his left sided molars was also attributed to GTS. Clonidine (up to 0·3 mg/day) produced substantial improvement in tic symptoms over the next year, although pronounced exacerbations were seen during times of stress or excitement, or after missing a medication dose.

PROGRESSION

At the age of 12 years and 6 months he developed frequent and forceful leg and hand tapping (more on the left), overt tongue thrusting, leftward head jerks, and a compulsion to hit nearby people. He also developed infrequent bitemporal throbbing headaches, thought to be migraines. Two months later an EEG showed independent sharp wave transients bilaterally, greater in the left anterior quadrant, which were attributed to migraines. His grades deteriorated from As and Bs to mostly Cs. His worsening tics, aggression, and poor school performance were attributed to GTS. Two months later, at the age of 13 years and 6 months, recurrence of seizures was characterised by left arm stiffening and ataxic speech, followed by left arm clonus. MRI then disclosed his tumour.

TUMOUR DESCRIPTION

His MRI (fig 2A and B) showed a 6 × 6 × 10 cm left parietal tumour involving the corpus callosum (isthmus, posterior, and midbody, seeming to cross the midline posteriorly), the body and isthmus of the left cingulate gyrus, the fornix, and the body and tail of the left caudate nucleus. The temporal and occipital horns of the lateral ventricles were moderately dilated due to obstructive hydrocephalus at the level of the atrium. The tumour was partially resected through a left parietal craniotomy. Histology showed a mixed oligodendroglioma and astrocytoma with anaplastic features. Radiotherapy at the age of 14 was unhelpful. Seizures continued, and the tumour quickly infiltrated through the cerebrum.

OUTCOME

In the year after discovery of the tumour, he developed hyperacusis and cold intolerance. Several strokes contributed to rapid clinical decline, and he died at the age of 15.

Case 3

A right handed boy with GTS, OCD, and ADHD developed a midbrain glioma and a recurrent major depressive illness.

EARLY INTRAMORBID COURSE

At the age of 4 this boy was evaluated with psychological testing for frequent nightmares and depression. He exhibited frequent eye-blinking, facial grimacing, and arm jerks. No vocal tics were yet evident. His IQ was normal, but severe visual-motor and fine motor control deficits were seen. He was also impulsive, perseverative, inattentive, and motorically hyperactive, meeting DSMIII-R criteria for ADHD.

A                                    B

Neurological evaluation at the age of 7 for ADHD confirmed these findings. A head CT and an EEG were both normal. Stimulants were not prescribed because of the presence of tics. At the age of 10 the neurologist again evaluated him for increasingly frequent migrainous headaches, associated with nausea and vomiting, that had been present since the age of 4. A repeat EEG was normal.

FAMILY AND DEVELOPMENTAL HISTORY
Family history included GTS in the patient's father and possible motor and phonic tics in his paternal grandmother. No family member had ADHD or OCD. Early childhood paediatric evaluations suggested mild motor developmental delays. He evidenced separation anxiety during most of his childhood.

GTS AND OCD SYMPTOMS
At the age of 11, as the frequency of migrainous headaches increased, tics also increased in frequency and forcefulness. By the end of that year, tics were incapacitating and nearly constant. He had numerous frequent motor and vocal tics that included eyeblinking, eyebrow raising, facial grimacing, lip pouting, head jerks, finger, arm, and leg jerking, abdominal tensing, nose rubbing, arm extension, sniffing, throat clearing, high pitched humming, and echolalia. Symptoms of OCD were severe, and included frequent checking, ordering, and evening up compulsions, list making, and ritualised behaviours. Clonidine (0·25 mg/day) was unhelpful for his tic and ADHD symptoms.

PROGRESSION
By the age of 12, the boy was complaining of worsening headaches, frequent nausea and vomiting, and acoustic hypersensitivity. Symptoms of OCD and GTS remained severe. Because of the persistence of frequent headaches, a brain MRI was obtained at the age of 12 years and 4 months.

TUMOUR DESCRIPTION
Brain MRI showed that a right tectal lesion

was obstructing the cerebral aqueduct, producing hydrocephalus of the lateral and third ventricles. The lesion involved the periaqueductal grey, right red nucleus, and right posteroinferior thalamus. A ventriculoperitoneal shunt was placed through the right parietooccipital lobe junction, through the white matter of the parietal lobule into the centrum semiovale and the right lateral ventrical. After shunt placement, headaches and vomiting persisted but were attributed to migraines.

SYMPTOM PROGRESSION
The boy's tics worsened in frequency and intensity over the next six months, and his OCD symptoms became intolerable. Pimozide (3 mg/day) was unhelpful for his tics. Serial scans in the next six months showed no evidence of recurrent hydrocephalus, although a gradually increasing tumour size was seen late in his 12th year, extending from the right quadrigeminal plate into the right posteroinferior hemithalamus, with calcification of the pulvinar. Despite enlargement, the tumour was believed to be benign. Phenytoin produced remarkable headache relief. Tic and OCD symptoms continued to be severe. At the age of 13 he developed an affective illness that met DSMIII-R criteria for major depression. He made three unsuccessful suicide attempts. Antidepressant trials were unhelpful.

At the age of 14, recurrent headaches, vomiting, and repeat CT indicated recurrent hydrocephalus, prompting three shunt revisions. Headaches, nausea, and vomiting returned at the age of 15. An MRI (fig 3A) at the age of 15 years and 5 months suggested tumour growth and perhaps low grade malignancy, with involvement of the posterior portion of the right red nucleus and possible anterior extension into the right subthalamic nucleus. Carboplatinum and vincristine chemotherapy was initiated but tumour growth continued over the next six months. A course of radiation therapy then arrested tumour progression by the age of 16 years and 2 months. He was still incapacitated by OCD symptoms despite treatment with 40 mg/day fluoxetine.

## Patient 1

1  2  7  8  9  10  11

Tumour diagnosis — Aggression — Enuresis — Tics appear — Tumour growth — Surgery — Tics disappear — Compulsions appear — Tumour and ↑OCD growth sx — Chemo and radiation — OCD sx improve

## Patient 2

7  8  9  10  11  12  13  14  15  16

Premorbid OCD sx — Tics appear — Enuresis — Focal seizures — Eye movements, neck dystonia; EEG transients, dx GTS — Acute GTS sx↑ — Tongue thrusting — Complex tics and aggression — ↑Migraines, EEG abnormal — Academic decline — Seizures and tumour recur — Tumour growth and GTS sx↑ — Death

## Patient 3

4  5  6  7  8  9  10  11  12  13  14  15  16  17

Tic sx and ADHD — Normal CT and EEG — ↑Migraines, ↑tic sx normal EEG — dx GTS and OCD — ↑Nausea and vomiting, migraines — Tumour found — ↑Tic and OCD sx — Tumour growth — Depression — Tumour growth — Chemo and radiation — Tumour growth arrested — ↑GTS and OCD sx
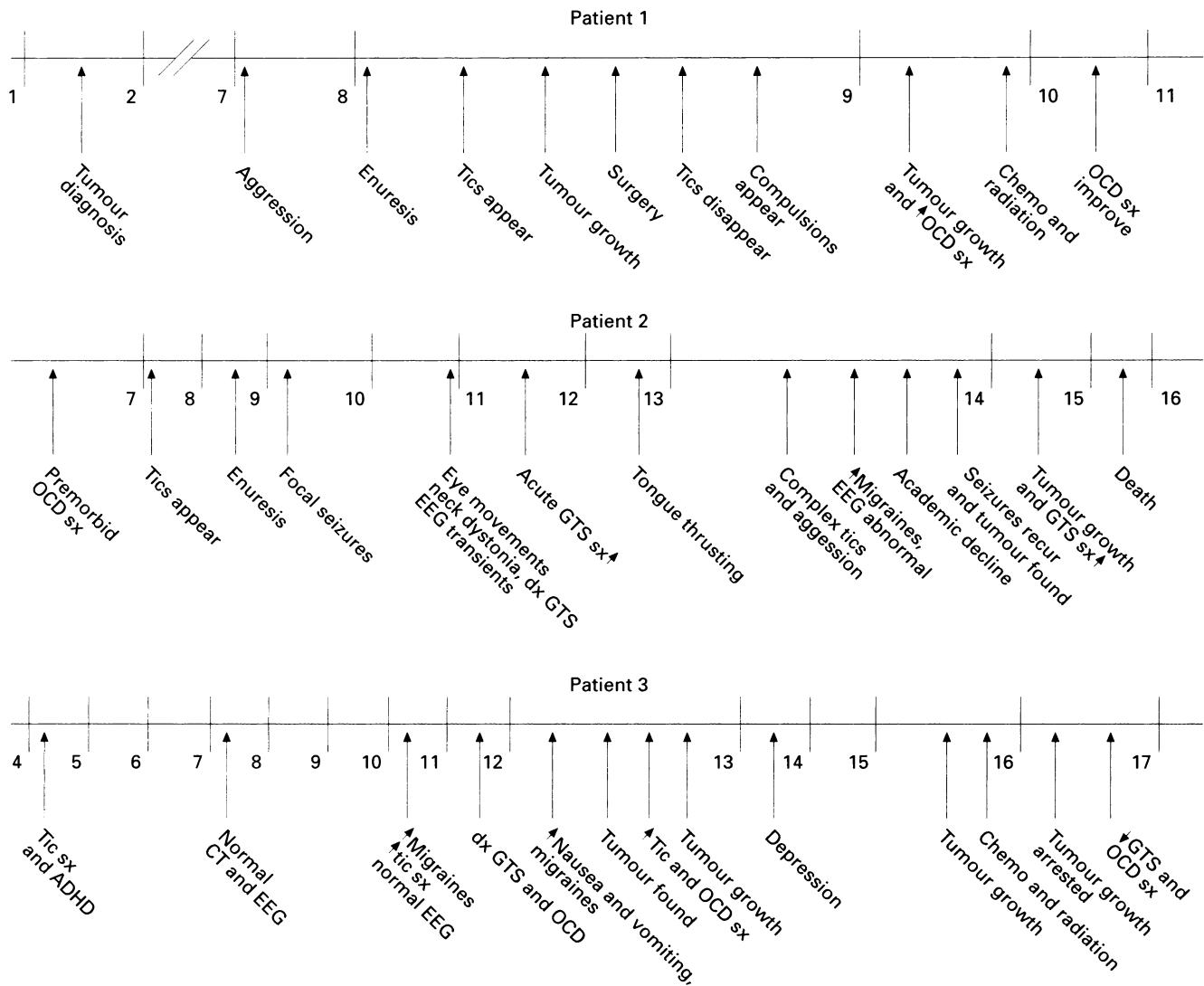
*Figure 4  Time line of tumour and symptom progression for each of the three cases. Details appear in the text. OCD sx = obsessive compulsive disorder symptoms; GTS sx = Gilles de la Tourette's symptoms.*

### OUTCOME

Tumour size remained stable, with continued involvement of the inferior and superior colliculi, the right red nucleus, and a slightly larger portion of the right pulvinar nucleus (fig 3B). Tic and OCD symptoms gradually but progressively improved between the ages of 16 and 17. Currently, at 21 years of age, motor tics are mild, and phonic symptoms are absent. Mild OCD symptoms persist. He is off all medication and attends a community college.

### Discussion

This is the first report of changes in symptoms of GTS and OCD associated with cerebral malignancies. Only one other report has associated GTS with an intracranial tumour[3] and we know of no cases of cerebral malignancy associated with OCD. In each of the present cases, symptoms changed with tumour progression and with either effective treatment or clinical demise (fig 4). All three children may have had a genetic diathesis to GTS or OCD, and their neuropsychiatric symptoms (particu-

larly in cases 2 and 3) antedated by several years the discovery of the tumours; it is therefore unlikely that the malignancies caused the neuropsychiatric symptoms. The symptoms of each child nevertheless increased during periods of rapid tumour growth or decreased soon after successful treatment, providing an opportunity to correlate symptom change with changes in tumour size and location that occur within a context of GTS and OCD illness or diathesis. These lesion correlates of symptom change can therefore help confirm and extend current theories of GTS and OCD neurobiology.

### GTS NEUROBIOLOGY

Although the cause of GTS is still unknown, it is thought to have strong genetic determinants.[4 5] Family studies suggest that the vulnerability to GTS is transmitted as a single major gene that can be variably expressed as either GTS or as OCD.[1] The specific genetic loci conferring this vulnerability have yet to be elucidated. It is currently unclear whether ADHD is also an alternative expression of this same vulnerability gene.[6 8] The effects of genetic and non-genetic determinants in GTS

and GTS related OCD are thought to be mediated through the basal ganglia and associated corticostriato-thalamocortical (CSTC) circuitry.[9-11] Evidence for basal ganglia involvement in GTS derives primarily from postmortem case reports and in vivo imaging studies showing hypoplasia and hypometabolism of GTS basal ganglia.[12-18]

NORMAL CSTC CIRCUITRY
Circuits in the CSTC are composed of multiple loops that direct information from the cerebral cortex to the subcortex, and then back again to specific regions of the cortex. Within each of these loops, information seems to be directed from multiple but functionally related cortical areas into specific portions of the subcortex—firstly, the striatum, then the globus pallidus (or substantia nigra pars reticulata), then to specific thalamic nuclei—before returning to the cortex.[19-21] These circuits are of central importance in the normal control of motoric, cognitive, and affective functioning. The tumours in each of the children described here likely altered GTS and OCD symptom severity by affecting the functioning of one or more portions of this circuitry.

CLINICOPATHOLOGICAL CORRELATIONS FOR GTS SYMPTOMS
Despite the differing tumour locations in each of these children, it is noteworthy that they all had prominent midline lesions, and that in two cases a change in symptom level was associated with corpus callosum and cingulate lesions, whether from tumour or surgery. In addition to these common anatomical features, the temporal sequences of changes in anatomical involvement seem to correlate with the development of specific behaviours in ways that are consistent with previous clinical and preclinical studies of GTS and OCD (table).

CASE 1
This girl's tic symptoms permanently disappeared after excision of her tumour and surgical lesion of the body of her right cingulate gyrus, her anterior corpus callosum, and the neighbouring interhemispheric sensorimotor fibres.

*Ventral striatum*
It is possible that her left sided facial tics were produced by tumour involvement of either her right sided ventral striatum or right amygdala. Unilateral electrical or chemical stimulation of the basal ganglia or the amygdala have been reported to produce tic-like stereotypies and vocalisations in animals and humans.[22-23] Amygdala stimulation produces primarily ipsilateral facial movements, however, and the greater extent of this girl's tumour was contralateral to her tics, which would suggest that her tics were not due to involvement of the amygdala. Anterior corpus callosum lesions in animals, moreover, fail to abolish the facial movements induced by amygdala stimulation,[22] so that the disappearance of this girl's tics after callosotomy strongly suggests that her hemifacial tics were produced by tumour involvement of her contralateral ventral striatum, and not her amygdala.

*Corpus callosum and cingulate*
It is improbable that partial evacuation of this girl's tumour would have completely relieved her tic symptoms. It seems more likely that the callosal and cingulate lesions eliminated her tics, for two reasons: (1) one imaging study has reported decreased corpus callosum size in patients with GTS, with a smaller corpus callosum correlating with decreasing severity of symptoms, suggesting that reduction in size of the corpus callosum may be compensatory in GTS and not necessarily pathogenic[24]; (2) preclinical studies of basal ganglia function in animals suggest that an intact corpus callosum is necessary for normal basal ganglia functioning.[25] It is possible, therefore, that the corpus callosum surgical lesion disrupted the known interhemispheric connectivity of the basal ganglia bilaterally,[20 21 26] and that this connectivity was necessary for the expression of the left sided tics due to the irritative lesion of her right ventral striatum.

The cingulate lesion may also have pro-

*Hypothesised regional neurobiological substrate of GTS and OCD, and the regions that are thought to modulate them. The lesions of each child and the symptoms that are postulated to be either affected or caused by them are cross tabulated with these regions. Further details appear in the text*

| Neurobiological substrate | Regions | PATIENT 1 | | PATIENT 2 | | PATIENT 3 | |
|---|---|---|---|---|---|---|---|
| | | Lesions | Symptoms | Lesions | Symptoms | Lesions | Symptoms |
| Hypothesised central to GTS | *CSTC circuits* Basal ganglia Subthalamic Thalamus nucleus Supplementary and premotor cortices Corpus callosum | Ventral striatum R > L Thalamus | L-sided facial tics Vocal tics? | Corpus callosum L caudate | Motor and phonic tic symptom exacerbation Conjugate eye movements and neck dystonia Tongue thrusting | R posterior hemithalamus R subthalamic nucleus | GTS and OCD symptom exacerbation? |
| Hypothesised central to OCD | *Limbic circuits* Cingulate gyrus Hypothalamus Amygdala Fornix | R cingulate (retractor induced) Hypothalamus Amygdala Fornix | Hyperphagia Bizarre compulsions Circadian dysrhythmia | L cingulate Fornix | Complex tics Aggressive motor tics | | Checking ordering, evening up and rituals |
| Modulating regions | *Brainstem* Periaqueductal grey Locus coeruleus Ventral tegmentum Substantia nigra Dorsal raphe | Ascending monoaminergic projections | Vocalisations? | | Hyperacusis | Periaqueductal grey Locus coeruleus Ventral tegmentum Substantia nigra Dorsal raphe R red nucleus Superior colliculi | GTS and OCD symptom exacerbation? Hyperacusis |

duced improvement in her tic symptoms. Electrical stimulation of of the anterior cingulate in humans produces semi-involuntary movements similar to complex motor tics,[27][28] and anterior cingulotomies have been reported, in uncontrolled studies, to alleviate tic symptoms in some patients.[29][30] The portion of the cingulate that was damaged by the retractor in this girl, moreover, is the portion which receives afferent projections from the motor cortex.[31]

## CASE 2
### Corpus callosum and cingulate

This boy's changes in symptom severity also seem to have been related to tumour involvement of the corpus callosum and cingulate, but this time primarily to the left of midline. Interhemispheric fibres topographically associated with the sensorimotor strip, and those associated with the parietal cortex, were most prominently involved. Whereas surgical lesions in the corpus callosum in the first patient apparently reduced tic symptoms by interrupting the interhemispheric transfer of irritative stimuli, the presence of tumour in this boy may have produced symptom exacerbation by producing an irritative focus within interhemispheric sensorimotor fibres. Although involvement of the the left caudate nucleus may also have produced tic exacerbation in this patient, it seems more likely that the caudate's greater connectivity to frontal and association cortices produced his new, more complex tics (his repetitive tapping and hitting).[9]

## CASE 3

This boy's tumour involved primarily the tectum of the midbrain at the level of the superior colliculus, and it extended dorsally into the venteroposterior thalamus. Midbrain lesions induced by encephalitis lethargica have previously been associated with GTS,[32] and have been hypothesised to disturb dopaminergic pathways ascending from the substantia nigra pars compacta ($SN_c$) and the ventral tegmental area (VTA). If the presence of tumour exacerbated tic symptoms in this patient, however, then its tectal location (in the dorsum of the midbrain, away from the $SN_c$ and VTA) would suggest that the nigra and ventral tegmentum were not involved, and that the mechanism of exacerbation was not due to disruption of ascending dopaminergic fibres. Rather, tic exacerbation due to involvement of tectal structures such as the superior colliculus and periaqueductal grey seems more plausible.

### Superior colliculus

The superior colliculus receives heterogeneous, multimodal, and topographically ordered inputs from visual and auditory centres, motor cortex, and other brainstem regions that are hypothesised to subserve its role in the orienting response.[33] Efferent pathways from the colliculus receive and integrate sensory stimuli, and then project to premotor cortical portions of CSTC circuits, which could explain an influence on tic symptoms

from this location. Situated just ventral to the superior colliculus, furthermore, is the mesencephalic nucleus of the fifth cranial nerve, a nucleus that relays unconscious proprioceptive information from the face. Disturbing this relay could affect the reflex reactivity of muscle spindles in the face, the region most commonly affected by tics in this boy and in most patients with GTS.

### Periaqueductal grey

Symptom exacerbation could also be due to involvement of the periaqueductal grey (PAG) matter, a vaguely defined cell mass that is continuous rostrally with the ventromedial and lateral hypothalamus and caudally with the dorsal raphe nucleus. Stimulation of the PAG can produce a wide array of behavioural responses, including sexual behaviours, vocalisation of emotion, aggressive and defensive posturing, and activation of the sympathetic nervous system,[34] similar to many of the tic related behaviours seen in GTS. Disturbances in the PAG previously have been hypothesised to underlie the production of motor and vocal tics associated with encephalitis lethargica.[32] In addition, noradrenergic fibres ascending from the locus coeruleus pass through the PAG and probably were disrupted by this boy's tumour,[35] which may have worsened his symptoms. A similar mechanism of symptom exacerbation was postulated in an adult male patient with GTS whose PAG was calcified by a pineal tumour.[3]

### Thalamus

The extension of this tumour, and that of the first patient, into the venteroposterior portion of the thalamus, complements a series of neurosurgical case reports in which thalamic lesions attenuated tic symptoms.[36-41] By contrast with the destructive, non-irritative surgical lesions, the thalamic tumour involvement in these children more likely produced focal irritation. Venteroposterior regions of the thalamus and its subdivisions are an integral portion of the CSTC pathways carrying information for motor programmes that probably participate in tic symptom formation. An irritative focus anywhere along this pathway is prone to produce pathological transmission of information that it carries.

## CLINICOPATHOLOGICAL CORRELATIONS FOR OCD SYMPTOMS

Common to all three children, other than the midline location of their tumours, was the involvement of structures that are limbic system components: in patient 1, it was the hypothalamus, accumbens, and fornices from the tumour, and the body of the cingulate from surgery; in patient 2, it was the body of the cingulate and the fornices; and in patient 3, it was the PAG, which has strong and integral connections with the hypothalamus and cingulate. Tumours involved the caudate nucleus in two of the patients. These structures—the caudate nucleus and other basal ganglia structures, the cingulate and other limbic system components, and their connections with the

frontal cortex—have been hypothesised to comprise a disinhibited, reverberating neural circuit that gives rise to symptoms of OCD.[42]

*Cingulate*

It is noteworthy that whereas surgical lesions of the anterior cingulate gyrus are thought to alleviate symptoms of OCD in a substantial number of subjects refractory to pharmacotherapy,[43] the retractor lesion in the body of the right cingulate in patient 1 and the involvement of the body of the cingulate in patient 2 were both associated with the onset or progression of compulsive behaviours. Perhaps differing locations of lesions within the cingulate produce differential effects on symptoms with OCD, with anterior lesions improving, and more posterior lesions exacerbating, OCD symptoms.

*Hypothalamus*

The cingulate gyrus and hypothalamus are integrally interconnected, and both have been implicated in OCD and compulsive behaviours. The hypothalamus, for instance, is the site of oxytocin production, and oxytocin concentrations have been shown to be increased in OCD that is not genetically related to GTS.[44] Oxytocin is one of the mediators of numerous behaviours that are subserved by hypothalamic functioning and that could be considered phylogenetically conserved precursors to the content of common obsessions and compulsions. Oxytocin mediates behavioural aspects of grooming, maternal care and affiliation, and sexual and aggressive behaviours, all of which are components of common obsessive-compulsive symptoms.[45]

*Caudate nucleus*

The tumours of patients 1 and 2 also involved the caudate nucleus, which in neuroimaging studies has been implicated in OCD pathophysiology. Caudate nucleus hypermetabolism that has been seen in patients with OCD seems to normalise in response to effective treatment, which may suggest that the caudate nucleus is involved in either generation or supression of symptoms of OCD.[46-48] The destruction of the caudate nuclei by tumour in these two patients may have produced impaired inhibitory responses to impulses that are normally suppressed, thereby releasing, or disinhibiting, obsessive thoughts and compulsive behaviours.

**Conclusion**

The few patients in this series, the compromise of multiple brain regions by tumour, and the likely compromise of additional brain regions by microscopic tumour infiltration, oedema, and hydrocephalus all limit the conclusions that can be drawn concerning the anatomical localisation of the neural substrate of tic and OCD symptoms. The structures invaded by these tumours are nevertheless those implicated in the pathogenesis of GTS and OCD, both in theory and in previous clinical and preclinical studies. Midline structures,

including the corpus callosum, thalamus, brainstem, and limbic system, particularly the hypothalamus and cingulate, are the structures involved commonly in these three patients. The ventral basal ganglia, corpus callosum, thalamus, and brainstem seem to be primarily involved in tic symptom formation and modulation, whereas the hypothalamus, cingulate, and possibly caudate nucleus are likely predominantly involved in formation and modulation of symptoms of OCD. All these structures are either components of CSTC circuitry or else functionally modulate it through intimate neuroanatomical connections. This common neurobiological substrate may mediate the genetic relatedness of GTS and OCD and thereby explain their common clinical comorbidity. The portions of CSTC circuitry that are affected, or the neuromodulatory circuits that are compromised, may then determine which genetically vulnerable patients will develop GTS, OCD, or both.

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