し，臨床全般印象 Clinical Global Impressions (CGI) で著明改善または中等度改善が91%であった[49]．GTS成人患者でアリピプラゾールについて後方視的に検討したところ10名中3名で18カ月以上服用しても効果は持続した[50]．GTS小児・青年患者（7～14歳）を対象にオランザピンを6週間使用したオープン研究ではYGTSSの平均チック得点が30%減少し，CGIで著明改善または中等度改善が約2/3であった[51]．定型抗精神病薬であるピモジドの6つの臨床試験を再検討すると，プラセボと比較した3つの研究で有意差を認めるなどチックに有効なことが再確認された[52]．スルピリドについてGTSまたは慢性チック障害の小児・青年患者（3～15歳）で6週間使用して前方視的に検討したところ，YGTSSで有意な改善を認めたとの報告もある[53]．

非抗精神病薬の中で，トピラマートについては，後方視的なカルテ調査からGTS小児・青年患者367名中41名で服用しており薬物反応性を4段階で評価すると著明改善または中等度改善が75.6%であったとの報告[54]，GTS患者29名（平均16.5歳）で無作為二重盲検試験をしたところ20名で10週間を完了してYGTSSの平均チック得点の改善がプラセボよりもトピラマート（平均118mg/日服用）で有意に大きいなどチックや前駆衝動に有効であったとの報告[55]があり，期待される．レベチラセタムについては，GTS小児患者（平均12歳）に対する12週間のオープン研究で800～2000mg/日の服用でYGTSSでもCGIでも有意な改善を認めたとの報告[56]もある一方で，クロニジンと組み合わせてGTS小児・成人患者（8～27歳）で行った無作為二重盲検試験ではクロニジンと異なりYGTSSで有意な改善を認めなかったとの報告[57]もあり，評価が一定しない．

Ningdong顆粒を用いた8週間の無作為二重盲検試験ではGTS小児・青年患者（7～18歳）で平均チック得点の改善がプラセボ（10.8%）よりもNingdong（41.4%）で有意に大きい[58]など漢方薬の報告も出てきている．

G. 薬物以外の治療法

薬物以外の治療法としては脳深部刺激療法 deep brain stimulation (DBS) と認知行動療法が注目されている．DBSを受けたGTS患者39名の論文発表を踏まえて，難治患者に対してDBSが最も期待できる脳外科手法ではあるが，DBSによる利益を評価する際には併発症を考慮しなくてはならないとの指摘がある[59]．重症で治療抵抗性のGTS患者3名について視床の正中中心-束傍複合体 centromedian-parafascicular complex (CM-Pf) 及び淡蒼球内側（GPi）の両側に刺激電極を設置して効果を評価したところ，両側のGPiの刺激で劇的改善（YGTSSチック得点が65～96%の減弱），両側のCM-Pfの刺激で改善（30～64%の減弱）であったが，CM-PfとGPiを組み合わせても大差はなかった(43～76%の減弱)[60]．GTS患者2名について視床内側のDBSの長期間(6年及び10年)の転帰をみたところ，患者1では，治療から5年後に認められたチックの改善は10年後も維持されていたが，患者2では，治療から8カ月後のチックの改善は6年後にはやや低下していた．しかも患者2では認知の低下及び怒りと攻撃性の増加を認め，全般的な転帰を高めるには手術前から存在する心理社会的適応に手術後も配慮する必要があると示唆された[61]．

GTSまたは慢性チック障害の小児・青年患者126名(9～17歳)に無作為統制試験を行い，10週間で8セッションの包括的な行動療法（n＝61）または支持的治療と教育からなる対照の治療（n＝65）を行ったところ，ベースラインから最終時点までに行動療法（YGTSSで24.7から17.1）では対照群（24.6から21.1）と比べて有意に改

善を示した（effect size＝0.68）．CGIで著明改善または中等度改善が行動療法（52.5%）で対照群（18.5%）よりも高率であり，しかも行動療法に反応すると治療の6カ月後でも効果が持続していた[62]．GTSを含めた慢性運動チックの小児患者10名でチックの抑制に関する強化子の有無の影響を検討したところ，抑制の強化子があると有意にチックが少なく，様々な文脈での強化子の履歴がチックの表出の多様性を説明する可能性が示唆された[63]．破壊的行動を伴うGTS小児患者26名（平均12.7歳）を10セッションの怒りのコントロールトレーニング（ACT）または通常の治療に無作為に割り振ったところ，CGIで著明改善または中等度改善がACT（69%）では通常の治療（15%）よりも有意に高率であり，ACT群では3カ月後のフォローアップ時にも効果が継続していた[64]．GTS患者15名でGSRバイオフィードバックを行って交感神経系の覚醒とリラクセーションという2つの異なる生理的状態のチックへの影響をみると，チックは低減しており，バイオフィードバックリラクセーショントレーニングがチックに治療的役割を有する可能性が示唆された[65]．

H. GTS研究の展望

精神神経発達障害として多面的な検討の蓄積が進んでいる．例えば，DBSにしても認知行動療法にしても新しい治療の試みは自己制御にかかわる脳機能の調整を明確に目指しており，結果的にGTSの基盤にある脳機能の理解がいっそう深まる一方で，心理社会面の対応の重要性が確認されている．今後はさらに統合された研究が進むことが期待される．

文献

1) Morris CM, Pardo-Villamizar C, Gause CD, et al. Serum autoantibodies measured by immunofluorescence confirm a failure to differentiate PANDAS and Tourette syndrome from controls. J Neurol Sci. 2009; 276:45-8.
2) Freeman RD, Zinner SH, Müller-Vahl KR, et al. Coprophenomena in Tourette syndrome. Dev Med Child Neurol. 2009; 51: 218-27.
3) Mol Debes NM, Hjalgrim H, Skov L. Validation of the presence of comorbidities in a Danish clinical cohort of children with Tourette syndrome. J Child Neurol. 2008; 23: 1017-27.
4) Kano Y, Ohta M, Nagai Y, et al. Association between Tourette syndrome and comorbidities in Japan. Brain Dev. 2010; 32: 201-7.
5) Kano Y, Kono T, Shishikura K, et al. Obsessive-compulsive symptom dimensions in Japanese tourette syndrome subjects. CNS Spectr. 2010; 15: 296-303.
6) Haddad AD, Umoh G, Bhatia V, et al. Adults with Tourette's syndrome with and without attention deficit hyperactivity disorder. Acta Psychiatr Scand. 2009; 120: 299-307.
7) Burd L, Li Q, Kerbeshian J, et al. Tourette syndrome and comorbid pervasive developmental disorders. J Child Neurol. 2009; 24: 170-5.
8) Kerbeshian J, Peng CZ, Burd L. Tourette syndrome and comorbid early-onset schizophrenia. J Psychosom Res. 2009; 67: 515-23.
9) Cutler D, Murphy T, Gilmour J, et al. The quality of life of young people with Tourette syndrome. Child Care Health Dev. 2009 ; 35: 496-504.
10) Bernard BA, Stebbins GT, Siegel S, et al. Determinants of quality of life in children with Gilles de la Tourette syndrome. Mov Disord. 2009; 24: 1070-3.
11) Müller-Vahl K, Dodel I, Müller N, et al. Health-related quality of life in patients with Gilles de la Tourette's syndrome. Mov Disord. 2010; 25: 309-14.
12) Pringsheim T, Lang A, Kurlan R, et al. Understanding disability in Tourette syndrome. Dev Med Child Neurol. 2009; 51: 468-72.
13) Gorman DA, Thompson N, Plessen KJ, et al. Psychosocial outcome and psychiatric comorbidity in older adolescents with Tourette

syndrome: controlled study. Br J Psychiatry. 2010;197: 36-44.
14) Debes N, Hjalgrim H, Skov L. The presence of attention-deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder worsen psychosocial and educational problems in Tourette syndrome. J Child Neurol. 2010; 25: 171-81.
15) Altman G, Staley JD, Wener P. Children with Tourette disorder: a follow-up study in adulthood. J Nerv Ment Dis. 2009; 197: 305-10.
16) Robertson MM. The prevalence and epidemiology of Gilles de la Tourette syndrome. Part 1: the epidemiological and prevalence studies. J Psychosom Res. 2008; 65: 461-72.
17) Centers for Disease Control and Prevention (CDC). Prevalence of diagnosed Tourette syndrome in persons aged 6-17 years - United States, 2007. MMWR Morb Mortal Wkly Rep. 2009; 58: 581-5.
18) Eichele H, Eichele T, Hammar A, et al. Go/NoGo performance in boys with Tourette syndrome. Child Neuropsychol. 2010; 16: 162-8.
19) Thibault G, O'Connor KP, Stip E, et al. Electrophysiological manifestations of stimulus evaluation, response inhibition and motor processing in Tourette syndrome patients. Psychiatry Res. 2009; 167: 202-20.
20) Franzkowiak S, Pollok B, Biermann-Ruben K, et al. Altered pattern of motor cortical activation-inhibition during voluntary movements in Tourette syndrome. Mov Disord. 2010 Jul 28. [Epub ahead of print]
21) Heise KF, Steven B, Liuzzi G, et al. Altered modulation of intracortical excitability during movement preparation in Gilles de la Tourette syndrome. Brain. 2010; 133: 580-90.
22) Roessner V, Overlack S, Baudewig J, et al. No brain structure abnormalities in boys with Tourette's syndrome: a voxel-based morphometry study. Mov Disord. 2009; 24: 2398-403.
23) Plessen KJ, Bansal R, Peterson BS. Imaging evidence for anatomical disturbances and neuroplastic compensation in persons with Tourette syndrome. J Psychosom Res. 2009; 67: 559-73.
24) Fahim C, Yoon U, Das S, et al. Somatosensory-motor bodily representation cortical thinning in Tourette: effects of tic severity, age and gender. Cortex. 2010; 46: 750-60.
25) Müller-Vahl KR, Kaufmann J, Grosskreutz J, et al. Prefrontal and anterior cingulate cortex abnormalities in Tourette Syndrome: evidence from voxel-based morphometry and magnetization transfer imaging. BMC Neurosci. 2009; 10: 47.
26) Fahim C, Yoon U, Sandor P, et al. Thinning of the motor-cingulate-insular cortices in siblings concordant for Tourette syndrome. Brain Topogr. 2009; 22: 176-84.
27) Ludolph AG, Pinkhardt EH, Tebartz van Elst L, et al. Are amygdalar volume alterations in children with Tourette syndrome due to ADHD comorbidity? Dev Med Child Neurol. 2008; 50: 524-9.
28) Tobe RH, Bansal R, Xu D, et al. Cerebellar morphology in Tourette syndrome and obsessive-compulsive disorder. Ann Neurol. 2010; 67: 479-87.
29) Govindan RM, Makki MI, Wilson BJ, et al. Abnormal water diffusivity in corticostriatal projections in children with Tourette syndrome. Hum Brain Mapp. 2010 Feb 16. [Epub ahead of print]
30) Makki MI, Govindan RM, Wilson BJ, et al. Altered fronto-striato-thalamic connectivity in children with Tourette syndrome assessed with diffusion tensor MRI and probabilistic fiber tracking. J Child Neurol. 2009; 24: 669-78.
31) Thomalla G, Siebner HR, Jonas M, et al. Structural changes in the somatosensory system correlate with tic severity in Gilles de la Tourette syndrome. Brain. 2009; 132: 765-77.
32) Neuner I, Kupriyanova Y, Stöcker T, et al. White-matter abnormalities in Tourette syndrome extend beyond motor pathways. Neuroimage. 2010; 51: 1184-93.
33) Cavanna AE, Stecco A, Rickards H, et al. Corpus callosum abnormalities in Tourette syndrome: an MRI-DTI study of monozygotic twins. J Neurol Neurosurg Psychiatry. 2010; 81: 533-5.
34) Mazzone L, Yu S, Blair C, et al. An FMRI study of frontostriatal circuits during the inhibition of eye blinking in persons with Tourette syndrome. Am J Psychiatry. 2010; 167: 341-9.

35) Raz A, Zhu H, Yu S, et al. Neural substrates of self-regulatory control in children and adults with Tourette syndrome. Can J Psychiatry. 2009; 54: 579-88.
36) Church JA, Fair DA, Dosenbach NU, et al. Control networks in paediatric Tourette syndrome show immature and anomalous patterns of functional connectivity. Brain. 2009; 132: 225-38.
37) Albin RL, Koeppe RA, Wernette K, et al. Striatal [11C]dihydrotetrabenazine and [11C]methylphenidate binding in Tourette syndrome. Neurology. 2009; 72: 1390-6.
38) Steeves TD, Ko JH, Kideckel DM, et al. Extrastriatal dopaminergic dysfunction in tourette syndrome. Ann Neurol. 2010; 67: 170-81.
39) Saporta AS, Chugani HT, Juhász C, et al. Multimodality neuroimaging in Tourette syndrome: alpha-[11C] methyl-L-tryptophan positron emission tomography and diffusion tensor imaging studies. J Child Neurol. 2010; 25: 336-42.
40) Breedveld GJ, Fabbrini G, Oostra BA, et al. Tourette disorder spectrum maps to chromosome 14q31.1 in an Italian kindred. Neurogenetics. 2010 May 2. [Epub ahead of print]
41) Knight S, Coon H, Johnson M, et al. Tourette Syndrome Association International Consortium for Genetics. Linkage analysis of Tourette syndrome in a large Utah pedigree. Am J Med Genet B Neuropsychiatr Genet. 2010; 153B: 656-62.
42) Zimprich A, Hatala K, Riederer F, et al. Sequence analysis of the complete SLITRK1 gene in Austrian patients with Tourette's disorder. Psychiatr Genet. 2008; 18: 308-9.
43) Herzberg I, Valencia-Duarte AV, Kay VA, et al. Association of DRD2 variants and Gilles de la Tourette syndrome in a family-based sample from a South American population isolate. Psychiatr Genet. 2010; 20: 179-83.
44) Dehning S, Müller N, Matz J, et al. A genetic variant of HTR2C may play a role in the manifestation of Tourette syndrome. Psychiatr Genet. 2010; 20: 35-8.
45) Ercan-Sencicek AG, Stillman AA, Ghosh AK, et al. L-histidine decarboxylase and Tourette's syndrome. N Engl J Med. 2010; 362: 1901-8.
46) Chou IC, Lin HC, Wang CH, et al. Polymorphisms of interleukin 1 gene IL1RN are associated with Tourette syndrome. Pediatr Neurol. 2010; 42: 320-4.
47) Sundaram SK, Huq AM, Wilson BJ, et al. Tourette syndrome is associated with recurrent exonic copy number variants. Neurology. 2010; 74: 1583-90.
48) Budman C, Coffey BJ, Shechter R, et al. Aripiprazole in children and adolescents with Tourette disorder with and without explosive outbursts. J Child Adolesc Psychopharmacol. 2008; 18: 509-15.
49) Lyon GJ, Samar S, Jummani R, et al. Aripiprazole in children and adolescents with Tourette's disorder: an open-label safety and tolerability study. J Child Adolesc Psychopharmacol. 2009; 19: 623-33.
50) Kawohl W, Schneider F, Vernaleken I, et al. Aripiprazole in the pharmacotherapy of Gilles de la Tourette syndrome in adult patients. World J Biol Psychiatry. 2009; 10: 827-31.
51) McCracken JT, Suddath R, Chang S, et al. Effectiveness and tolerability of open label olanzapine in children and adolescents with Tourette syndrome. J Child Adolesc Psychopharmacol. 2008; 18: 501-8.
52) Pringsheim T, Marras C. Pimozide for tics in Tourette's syndrome. Cochrane Database Syst Rev. 2009; (2): CD006996.
53) Ho CS, Chen HJ, Chiu NC, et al. Short-term sulpiride treatment of children and adolescents with Tourette syndrome or chronic tic disorder. J Formos Med Assoc. 2009; 108: 788-93.
54) Kuo SH, Jimenez-Shahed J. Topiramate in treatment of tourette syndrome. Clin Neuropharmacol. 2010; 33: 32-4.
55) Jankovic J, Jimenez-Shahed J, Brown LW. A randomised, double-blind, placebo-controlled study of topiramate in the treatment of Tourette syndrome. J Neurol Neurosurg Psychiatry. 2010; 81: 70-3.
56) Fernández-Jaén A, Fernández-Mayoralas DM, Muñoz-Jareño N, et al. An open-label, prospective study of levetiracetam in children and adolescents with Tourette syndrome. Eur J

Paediatr Neurol. 2009; 13: 541-5.
57) Hedderick EF, Morris CM, Singer HS. Double-blind, crossover study of clonidine and levetiracetam in Tourette syndrome. Pediatr Neurol. 2009; 40: 420-5.
58) Zhao L, Li AY, Lv H, et al. Traditional Chinese medicine Ningdong granule: the beneficial effects in Tourette's disorder. J Int Med Res. 2010; 38: 169-75.
59) Porta M, Sassi M, Ali F, et al. Neurosurgical treatment for Gilles de la Tourette syndrome: the Italian perspective. J Psychosom Res. 2009; 67: 585-90.
60) Welter ML, Mallet L, Houeto JL, et al. Internal pallidal and thalamic stimulation in patients with Tourette syndrome. Arch Neurol. 2008; 65: 952-7.
61) Ackermans L, Duits A, Temel Y, et al. Long-term outcome of thalamic deep brain stimulation in two patients with Tourette syndrome. J Neurol Neurosurg Psychiatry. 2010 Jul 26. [Epub ahead of print]
62) Piacentini J, Woods DW, Scahill L, et al. Behavior therapy for children with Tourette disorder: a randomized controlled trial. JAMA. 2010; 303: 1929-37.
63) Woods DW, Walther MR, Bauer CC, et al. The development of stimulus control over tics: a potential explanation for contextually-based variability in the symptoms of Tourette syndrome. Behav Res Ther. 2009; 47: 41-7.
64) Sukhodolsky DG, Vitulano LA, Carroll DH, et al. Randomized trial of anger control training for adolescents with Tourette's syndrome and disruptive behavior. J Am Acad Child Adolesc Psychiatry. 2009; 48: 413-21.
65) Nagai Y, Cavanna A, Critchley HD. Influence of sympathetic autonomic arousal on tics: implications for a therapeutic behavioral intervention for Tourette syndrome. J Psychosom Res. 2009; 67: 599-605.

Rage Attacks and Aggressive Symptoms in Japanese Adolescents with Tourette Syndrome

By Yukiko Kano, MD, PhD, Masataka Ohta, MD, PhD, Yoko Nagai, PhD, Ian Spector, and Cathy Budman, MD

ABSTRACT

Objective: This study was conducted to explore possible causes of rage attacks as well as clinically significant aggressive symptoms in Japanese adolescents with Tourette syndrome (TS).

Methods: The subjects included 29 adolescents (23 males, 6 females; mean age: 13.5±3.7 years). Eighteen subjects (62.1%) were diagnosed with TS only, 11 (37.9%) with TS and comorbidities, including attention-deficit/hyperactivity disorder and obsessive-compulsive disorder. Parents completed the Child Behavior Checklist. Clinically significant aggressive symptoms were assessed using two pilot tools, the Rage Screen and Questionnaire and the Clinical Rating of Aggression.

Results: Thirteen subjects (44.8%) were judged to have clinically significant aggressive symptoms, according to the Clinical Rating of Aggression. Twelve met criteria for recurrent rage attacks, according to the Rage Screen and Questionnaire. Between the 13 aggressive and 16 non-aggressive subjects, no significant differences were found in age, gender, psychiatric comorbidities, or concurrent medication. Child Behavior Checklist ratings to compare 11 aggressive and 12 non-aggressive subjects ≤16 years of age revealed elevated *t*-test scores on the anx-

Needs Assessment

Tourette syndrome (TS) is a neuropsychiatric disorder of childhood onset characterized by multiple motor and vocal tics that wax and wane in severity. Recurrent explosive outbursts ("rage attacks") and other aggressive symptoms in TS are a leading cause of morbidity for patients and their families. It seems that such symptoms are often secondary to comorbid psychiatric disorders in TS. There is a need to better recognize, characterize, and properly treat aggression in TS.

Learning Objectives

At the end of this activity, the participant should be able to:

- Identify explosive outbursts as a common symptom of impulsive aggression that occurs among clinical populations of children with Tourette syndrome (TS) worldwide.
- Recognize certain types of internalizing and externalizing behaviors that seem associated with explosive outbursts in Japanese adolescents with TS.
- Recognize that explosive outbursts and related behaviors as well as tics should be considered in treatment for TS.

Target Audience: Neurologists and psychiatrists

CME Accreditation Statement

This activity has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Mount Sinai School of Medicine and MBL Communications, Inc. The Mount Sinai School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

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This activity has been peer-reviewed and approved by Eric Hollander, MD, chair at the Mount Sinai School of Medicine. Review date: March 17, 2008. Dr. Hollander does not have an affiliation with or financial interest in any organization that might pose a conflict of interest.

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Dr. Kano is specially appointed associate professor in the Department of Child Psychiatry at The University of Tokyo Hospital in Tokyo, Japan. Dr. Ohta is president and Dr. Nagai is vice president of the Institute for Development of Mind and Behavior in Tokyo. Mr. Spector is a premed undergraduate student at Brown University in Providence, Rhode Island. Dr. Budman is associate professor in the Department of Psychiatry at North Shore Hospital-Long Island Jewish Health System in Manhasset, New York.

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Please direct all correspondence to: Yukiko Kano, MD, PhD, The University of Tokyo Hospital, Department of Child Psychiatry, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan; E-mail: kano-tky@umin.ac.jp.

ious/depressed, thought problems, aggressive, internalizing, externalizing subscales, and total scale in the aggressive group versus the non-aggressive group.

Conclusion: Rage attacks and clinically significant aggressive symptoms are common problems in Japanese TS youth. Psychiatric morbidity appears associated with impulsive-aggressive symptoms. Treatment implications from these findings need to be explored further.

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INTRODUCTION

Tourette syndrome (TS) is defined as a chronic tic disorder with multiple motor tics and one or more vocal tics. TS has a high prevalence of psychiatric comorbidities, including obsessive-compulsive disorder (OCD), and attention-deficit/hyperactivity disorder (ADHD), and mood disorders.[1] "Rage attacks" or "recurrent explosive outbursts" are a type of impulsive-aggressive symptom that is common in TS and often contributes to social morbidity. Rage attacks are defined using modifications of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-Text Revision*[2] criteria for intermittent explosive disorder. Discrete episodes of failure to resist aggressive impulses that result in serious assaultive acts or destruction of property, with a degree of aggressiveness expressed during the episodes that is grossly out of proportion to any precipitating psychosocial stressors, qualify as rage attacks.[2-4]

Previous studies[3-5] have suggested that rage attacks in children with TS are associated with the presence of comorbid disorders, namely ADHD, OCD, and oppositional defiant disorder. One study of aggression in children with TS,[6] using the Child Behavior Checklist (CBCL), reported that the group with TS and comorbid ADHD or OCD was significantly more aggressive than the control group, but there were no differences in aggression between the TS-only and control groups.[7]

The current investigation was conducted to clarify the possible conditions associated with both clinically significant aggression and the specific type of impulsive aggression defined as "rage attacks" in Japanese youth with TS. Differences in clinical symptomatology and psychotropic medication usage between Japanese adolescents with TS who display these impulsive-aggressive symptoms and those without were compared.

METHODS

Adolescents diagnosed with TS were consecutively recruited as subjects for study from two Japanese specialty neuropsychiatric clinics. The assessment battery was used as a part of standard clinical evaluation. All subjects and their parents provided written informed consent for participation in the study and all study subjects provided oral or written assent. Patients with neurologic disorders or other known causes of aggression or who had experienced a change in psychotropic medication within 4 weeks were excluded from the study.

The study population consisted of 29 patients (23 males, 6 females; mean age: 13.5±3.7 years, range: 8–21 years of age) diagnosed with TS by two experienced child psychiatrists (YK, MO), according to *DSM-IV-TR* criteria.[2] Eighteen patients (62.1%) were diagnosed with TS only and 11 patients (37.9%) with TS and comorbid disorders. Of these, 11 patients with TS and psychiatric comorbidities; five patients (17.2%) with TS and ADHD; another five (17.2%) with TS and OCD; and one (3.4%) with TS, ADHD, and learning disorders (Table 1).

Data regarding clinical characteristics related to tics, including age of tic onset, type and severity of each tic symptom, as well as obsessive-compulsive symptoms, self-injurious behaviors, and impulsivity, was collected through clinical interviews with the patients and their parents by the two child psychiatrists (YK, MO) as well as from data obtained in patient medical records. Information concerning psychotropics was provided by treating physicians. Diagnoses of OCD, ADHD, or other psychiatric comorbidities were established based on clinical assessment and chart review using *DSM-IV-TR* criteria.

Two surveys, the Clinical Rating of Aggression (CRA) (Y. Kano, MD, PhD, and M. Ohta, MD, PhD, unpublished rating scale, 2002) and the Rage Screen and Questionnaire (RSQ),[4] were used for the screening and evaluation of impulsive aggression to assess current and past rage attacks.

The RSQ explores the presence of clinically significant rage attacks that have occurred in the

past week to month prior to evaluation. Rage symptoms must meet a designated threshold for frequency (ie, minimum of 3 episodes per week or ≥4 episodes during a 1-month period of time) and intensity (ie, degree of aggressiveness expressed during the episodes are grossly out of proportion to any precipitating psychosocial stressors or frustration) to be considered present. Although not yet validated, the RSQ was translated into Japanese for the purpose of studying rage phenomenology in Japanese youth with TS with the authors' permission.[4] The rage screen portion was adapted to also assess the presence of clinically significant recurrent rage attacks in the past 6 months, provided that there was at least one period of ≥3 episodes per week or a minimum of 4 episodes per month during this time period.

The rage questionnaire portion explores possible clinical features that are associated with rage symptoms in children and adults with TS.

The CRA was developed by Kano and Ohta to specifically assess clinically significant impulsive aggression phenomenology that occurred within the 1 month prior to initial consultation. The CRA is being used as a global assessment of impact of physically and verbally aggressive behaviors toward other individuals and property and focuses on impairment of daily life. It consists of a Likert scale, with scores ranging from 1 (none) to 5 (most severe):

1. None: No aggression or, if any, impairment of social adjustment;
2. Mild: A certain degree of aggression but not particularly noticeable, and slight impairment in some areas of daily life, such as family, school, and peer relationship;
3. Moderate: Slightly noticeable aggression affecting ≥1 areas of daily life (periodic distress and upheaval in the family, frequent teasing by peers or social avoidance, periodic interference in school);
4. Severe: Conspicuous aggression causing serious impairment of daily activities, including family life, school life, and peer relationship;
5. Most Severe: Extremely conspicuous aggression, making daily life very difficult.

TABLE 1.
Demographic Findings and Diagnoses in Aggressive and Non-aggressive Japanese Youth with TS

	Aggressive Group (n=13)	*Non-aggressive Group (n=16)*
Gender ratio (M:F)	10:3	13:3
Mean age (years)	13.5±3.4	13.4±4.1
TS only	7 (53.8%)	11 (68.8%)
TS+ADHD	3 (23.1%)	2 (12.5%)
TS+OCD	2 (15.4%)	3 (18.8%)
TS+ADHD+LD	1 (7.7%)	0 (0%)
CBCL data available	11	12

TS=Tourette syndrome; M=male; F=female; ADHD=attention-deficit/hyperactivity disorder; OCD=obsessive-compulsive disorder; LD=learning disorder; CBCL=Child Behavior Checklist.

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The potential usefulness of the CRA was explored in this study to help acquire data regarding the clinical phenomenology of impulsive-aggressive symptoms in TS. However, the validity and reliability of neither the RSQ nor the CRA has been confirmed. Two experienced clinicians (YK, OH) had reached a high proficiency with RSQ and CRA ratings.

To assess a wide range of mental and behavioral problems in this study sample, the CBCL was completed by the subject's parents.[6] *t*-test scores of CBCL were calculated for subjects ≥16 years of age who completed this measure.

The Global Assessment of Functioning,[2] a standardized measure, was used to assess overall current social adjustment.

Overall tic severity was evaluated using the tic global severity rating of the Shapiro Tourette Syndrome Severity Scale (STSSS),[8] a 7-point rating scale of tic severity ranging from 0 (no tics) to 6 (extremely severe).

Statistical analysis used χ^2 test, Fisher's exact test, non-paired *t*-test, and Mann-Whitney test. Statistical significance was considered at $P<.05$.

RESULTS

Global-behavioral Problems and Social Adjustment

To determine global-behavioral problems related to impulsive-aggressive symptoms, the CRA was first used to determine clinically significant aggression that causes distress and impairment that the clinician, patient, and/or family

view as worthy of intervention in 23 patients with available CBCL data. Eleven (47.8%) subjects were found to have clinically significant aggression and 12 (52.2%) did not. Both groups were then assessed by CBCL in order to compare long-term psychiatric morbidities associated with clinically significant impulsive-aggressive symptoms. *t*-test scores were then computed for both groups for the anxious/depressed, thought problems, aggression, internalizing, externalizing, and total problems subscales (Table 2). Scores were significantly higher in the aggressive group than in the non-aggressive group (P=.003, P=.002, P=.020, P=.031, P=.031, P=.013, respectively, *t*-test).

The Global Assessment of Functioning scores were lower in the aggressive group (mean: 49.7±8.2) than in the non-aggressive group (mean: 55.0±7.7), although this finding did not meet statistical significance (P=0.083, *t*-test).

Characteristics of Tourette Syndrome Patients Who Have Had Clinically Significant Rage Attacks in the Past Six Months

Using the RSQ to explore the clinical features and phenomenology of rage attacks over the past 6 months, it was found that of the 19 TS patients who were reported to have had recurrent rage attacks within the past 6 months, 14 (73.7%) felt guilty about their behaviors or regretted their actions afterward, of whom 6 (31.6%) always had a guilty conscience.

Sixteen patients (84.2%) reported verbal attacks or abuse during outbursts of anger, 14 (73.7%) physically attacked other people and/or property, and 12 (63.2%) had both verbal and physical attacks. Eighteen patients (94.7%) reported having attacks at home, followed by four (21.1%) patients having attacks at school, and three (15.8%) patients experiencing attacks at home and at school. Seventeen patients (89.5%) out of 19 directed the attacks toward their mothers, followed by 13 (68.4%) toward inanimate objects (Table 3). Eighteen (94.7%) claimed that their anger was precipitated by being told that they were wrong about something, followed by 15 (78.9%) when they felt they failed to have their way.

Characteristics of Tourette Syndrome Patients Who Have Had Clinically Significant Aggressive Symptoms in the Past Month

Two experienced child psychiatrists rated overall aggressive symptoms in these TS patients according to the guidelines for the CRA. They found 16 TS patients (55.2%) with no signs of aggression, 6 (20.7%) as mildly aggressive, and 7 (24.1%) as moderately aggressive, for a total of 13 (44.8%) aggressive subjects. Across all subjects, there were no significant differences in age, gender, or diagnoses (Table 1).

Of the 13 patients with clinical symptoms of aggression over the past 1 month prior to

TABLE 2.
CBCL Subscores in Aggressive and Non-aggressive Japanese Youths with TS

Scales	*Aggressive Group (n=11)*	*Non-aggressive Group (n=12)*	t	P
I. Withdrawn	59.5±10.1	56.0±5.5	−1.002	.332
II. Somatic	58.5±8.5	56.6±7.8	−0.551	.587
III. Anxious/Depressed	68.9±9.2	57.8±6.9	−3.321	.003
IV. Social	61.2±7.4	56.9±6.2	−1.501	.148
V. Thought	72.4±10.1	57.3±9.9	−3.596	.002
VI. Attention	65.5±9.9	61.2±6.9	−1.210	.240
VII. Delinquent	65.6±8.8	58.3±9.2	−1.963	.063
VIII. Aggressive	68.5±9.0	59.2±8.7	−2.318	.020
IX. Internal	66.6±10.9	58.1±6.1	−2.320	.031
X. External	69.2±9.6	58.3±10.6	−2.706	.013
Total CBCL Score	70.6±10.4	60.1±8.2	−2.716	.013

CBCL=Child Behavior Checklist; TS=Tourette syndrome.

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entry, 12 (92.3%) experienced symptoms that met RSQ criteria for rage attacks (Table 4). The parents of the remaining patient failed to report symptoms severe enough to meet required RSQ criteria for rage attacks, but described impulsive-aggressive symptoms that were judged to be clinically significant according to the CRA. Seven (43.8%) out of 16 without aggression also reported to have had at least one rage attack in the past 6 months but did not meet frequency or impairment criteria for clinically significant aggression. Additionally, seven patients (53.8%) out of 13 with aggression and none (0%) out from the non-aggressive group were reported to have had rage attacks within the week prior to assessment, indicating a significant difference between the two groups (P=.005, Fisher's exact test). This suggests that the presence and frequency of rage attacks within the past week may be the most meaningful criterion for distinguishing patients with significant impairment due to aggression from those without.

There were no significant differences between subjects in the mean age at onset of tics, coprolalia, and obsessive-compulsive symptoms between the TS patients with aggression and those without (Table 5). However, a significant difference (P=.011, Fisher's exact test) was noted between the two groups with respect to self-injurious behaviors, which were observed only in the aggressive group. Both the worst and current levels of tic severity were higher in the aggressive group than in non-aggressive group, although these findings did not meet statistical significance (P=.068, P=.092, Mann-Whitney test).

Of the 29 total subjects, 19 were taking psychotropics. Haloperidol was the most common and was being taken by 10 subjects. Seven subjects were on pimozide, six were on fluvoxamine, and three were on risperidone (Table 6). There were no statistically significant differences in presence, absence, or type of concomitant psychotropics between the aggressive group and the non-aggressive group.

TABLE 3.
Targets and Precipitants of Attacks

	Respondents (N=19)
Targets of Attacks	
Mother	17 (89.5%)
Objects/things	13 (68.4%)
Siblings	11 (58.9%)
Father	10 (52.6%)
Precipitants of Attacks	
Told they were wrong about something	18 (94.7%)
Failure to get their way	15 (78.9%)
Change in routine or schedule	14 (73.7%)
Felt sense of frustration	11 (58.9%)
Told to give up on a task	10 (52.6%)
Felt imperfection	8 (42.1%)
Had a possession taken away	7 (36.8%)

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Comparison of Rage Attacks and Aggression Among Three Groups by Diagnoses

Rage attacks, aggression, and related symptoms were compared among three groups (ie, TS only, TS+ADHD, and TS+OCD). *t*-test scores of withdrawn, attention, and total problems subscales in CBCL and the rates of obsessive-compulsive symptoms and self-injurious behaviors were significantly different among the three groups. However, no significant differences were found in rage attacks rated by RSQ and aggression rated by CRA.

DISCUSSION

The findings from this naturalistic study suggest that in this particular sample of TS patients represented at a Japanese specialty clinic, rage attacks appear to occur rather commonly. TS patients with rage attacks in this sample seemed to have more psychiatric comorbidity than TS patients without such symptoms, but the difference between these two groups was smaller than expected based on earlier reports.[3]

Tic severity and self-injurious behaviors appeared associated with clinically significant aggressive symptoms in TS. This finding in our current study is in agreement with recent studies[9] that correlated self-injurious behaviors and tic severity with the presence of episodic explosive outbursts/rage attacks.

Data from the RSQ which was translated into Japanese revealed that the majority of subjects with rage attacks targeted their anger at their mothers. Rage attacks were also found to occur

at home far more frequently than at school. In our current study, "teasing and embarrassment," "no reason at all," and "having to compete with others for attention" were reported as precipitants of rage attacks in ≤20% responses.

As expected, the aggression subscale score of the CBCL was significantly higher in the clinically significant impulsive-aggressive TS group. However, subscales for anxiety/depression and thought problems on the CBCL also reached pathological levels that were significantly higher for the clinically aggressive TS group than in the non-aggressive TS group.

This is a descriptive study of aggressive symptoms studied in a small sample of Japanese youth with TS who presented for treatment at a speciality clinic. Our findings are limited by the primarily naturalistic, descriptive nature of the assessment tools that relied mostly on both child and parent reports, since it is uncommon for rage attack symptoms to be witnessed in the clinician's office. The findings from this study are also compromised by potential referral bias, since it was conducted at a specialty psychiatric clinic and its findings may not be generalizable to TS patients in the community. The data exam-

TABLE 4.
Relationship Between RSQ and CRA

	Aggressive Group (n=13)	Non-aggressive Group (n=16)	P
≥1 rage attacks in the past 6 months	12 (92.3%)	7 (43.8%)	.073
≥1 rage attacks within 1 week	7 (53.8%)	0 (0%)	.005

RSQ=Rage Screen and Questionnaire; CRA=Clinical Rating of Aggression.
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TABLE 5.
Clinical Phenomenology in Aggressive and Non-aggressive Japanese Youth with TS

	Aggressive Group (n=13)	Non-aggressive Group (n=16)	P
Mean age at onset of tics (years)	6.1±2.3	6.4±2.5	.721
Mean age at first visit (years)	13.0±3.3	12.1±3.5	.466
Coprolalia	5 (38.5%)	5 (31.3%)	.684
OCS	5 (38.5%)	6 (37.5%)	.958
Self-injurious behaviors	5 (38.5%)	0 (0%)	.011
Worst ever STSSS rating			.068
2	0 (0%)	1 (6.3%)	
3	2 (15.4%)	7 (43.8%)	
4	5 (38.5%)	4 (25.0%)	
5	4 (30.8%)	3 (18.8%)	
6	2 (15.4%)	1 (6.3%)	
Current STSSS rating			.092
1	0 (0%)	2 (12.5%)	
2	3 (23.1%)	6 (31.3%)	
3	5 (38.5%)	7 (43.8%)	
4	3 (23.1%)	2 (12.5%)	
5	2 (15.4%)	0 (0%)	

TS=Tourette syndrome; OCS=obsessive-compulsive symptoms; STSSS=Shapiro Tourette Syndrome Severity Scale.
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ining potential differences in current comorbidities between the two groups must be viewed with caution since this is a relatively small, uncontrolled sample of patients and the psychiatric diagnoses were not established using standardized structured measures but instead relied on clinical assessments using *DSM-IV-TR* criteria. In addition, this sample reflected youth with TS whose overall symptoms were of sufficient severity to require specialty assessment and intervention.

While there appeared to be evidence supporting the impression that frequency (rather than impairment in daily life) of rage attacks may be the most significant clinical characteristic to distinguish clinically meaningful impulsive-aggressive symptoms in TS from those that are not, the results of this small, uncontrolled pilot study must be viewed as suggestive and further follow-up studies are necessary. The small sample size in this study may be related to some difference between our findings and previous North American studies.[3,4,6,10,11] In addition, there seem to be less recognition and treatment of TS and its psychiatric comorbidities in Japan, although this is improving.

Although none of the subjects in the study met *DSM-IV-TR* criteria for an anxiety or mood disorder, anxious and depressive symptoms were found to be closely associated with clinically significant aggressive symptoms on CBCL. This is of interest, since aggressive behavior is frequently observed in adolescents with major depression, regardless of gender.[12] Other investigators have pointed out that boys with aggression and ADHD develop depressive symptoms more frequently and have lower self-esteem than those without aggressive symptoms,[13] again emphasizing the possible association between depression and aggression. It would be important to attempt to study rage and other aggressive symptoms in Japanese youth with TS by using structured validated interviews and measures, such as the Kiddie-Schedule for Affective Disorders and Schizophrenia,[14] that can better evaluate current and lifetime mood and anxiety disorders. Although no significant difference was found in the rates of OCD and obsessive-compulsive symptoms between aggression and non-aggression groups, precipitants of rage attacks suggested close relationship to obsessive-compulsive symptoms. Obsessive-compulsive symptoms should be assessed more precisely using formal, standardized rating scales and then examined in Japanese TS youth with and without aggression in future studies.

This study highlights the common problem of significant impulsive-aggressive symptoms, including rage attacks, in youth with TS who present for treatment at a specialty clinic in Japan and contributes to the growing body of literature that suggests that aggressive symptoms in TS are considerable causes of morbidity in this population worldwide. The phenomenology of aggressive symptoms in TS, their clinical correlates, and potential diagnostic and treatment strategies requires further attention.

TABLE 6.
Medication Status in Aggressive and Non-aggressive Japanese Youth with TS

Medication	Aggressive Group (n=13)	Non-aggressive Group (n=16)
Receiving any psychotropic medication	10 (76.9%)	9 (56.3%)
Antipsychotics	9 (69.2%)	9 (56.3%)
Haloperidol	6 (46.1%)	4 (25%)
Pimozide	4 (30.8%)	3 (18.8%)
Risperidone	0 (0%)	3 (18.8%)
SSRIs	4 (30.8%)	4 (25%)
Fluvoxamine	3 (23.1%)	3 (18.8%)
Paroxetine	1 (7.7%)	1 (6.3%)
Clomipramine	0 (0%)	1 (6.3%)
Clonidine	1 (7.7%)	1 (6.3%)

TS=Tourette syndrome; SSRIs=selective serotonin reuptake inhibitors.

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CONCLUSION

In Japanese TS adolescents, no significant differences were found in age, gender, or comorbidities by the presence or absence of aggression within 1 month of clinical identification by experienced child psychiatrists. Tic severity and self-injurious behaviors appeared associated with clinical significant aggression. When global behavioral problems were evaluated by CBCL, *t*-test scores of anxious/depressed, thought problems and aggression were significantly higher in aggressive subjects than in non-aggressive subjects.

This study suggested that aggression was associated with psychiatric symptoms, especially anxiety and depression, in Japanese adolescents with TS. Relationship among these symptoms should be confirmed by more rigorous methods. *CNS*

REFERENCES

1. Robertson MM. Mood disorders and Gilles de la Tourette's syndrome: an update on prevalence, etiology, comorbidity, clinical associations, and implications. *J Psychosom Res.* 2006;61:349-358.
2. *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed, text rev. Washington, DC: American Psychiatric Association; 2000.
3. Budman CL, Bruun RD, Park KS, Lesser M, Olson M. Explosive outbursts in children with Tourette's disorder. *J Am Acad Child Adolesc Psychiatry.* 2000;39:1270-1276.
4. Budman CL, Rockmore L, Stokes J, Sossin M. Clinical phenomenology of episodic rage in children with Tourette syndrome. *J Psychosom Res.* 2003;55:59-65.
5. Budman CL. Treatment of aggression in Tourette syndrome. *Adv Neurol.* 2006;99:222-226.
6. Stephens RJ, Sandor P. Aggressive behaviour in children with Tourette syndrome and comorbid attention-deficit hyperactivity disorder and obsessive-compulsive disorder. *Can J Psychiatry.* 1999;44:1036-1042.
7. Achenbach TM. *Manual for the Child Behavior Checklist/4—18 and 1991 profile.* Burlington, Vt: University of Vermont, Department of Psychiatry; 1991.
8. Shapiro AK, Shapiro E, Young JG, Feinberg TE. *Gilles de la Tourette Syndrome.* 2nd ed. New York, NY: Haven Press; 1988.
9. Mathews CA, Waller J, Glidden D, et al. Self injurious behaviour in Tourettes syndrome: correlates with impulsivity and impulse control. *J Neurol Neurosurg Psychiatry.* 2004;75:1149-1155.
10. Budman CL, Beuun RD, Park KS, Olson ME. Rage attacks in children and adolescents with Tourette syndrome. *J Clin Psychiatry.* 1998;59:576-580.
11. Freeman RD, Fast DK, Burd L, Kerbeshian J, Robertson MM, Sandor P. An international perspective on Tourette syndrome: selected findings from 3500 individuals in 22 countries. *Dev Med Child Neurol.* 2000;42:436-447.
12. Knox M, King C, Hanna GL, Logan D, Ghaziuddin N. Aggressive behavior in clinically depressed adolescents. *J Am Acad Child Adolesc Psychiatry.* 2000;39:611-618.
13. Treuting JJ, Hinshaw SP. Depression and self-esteem in boys with attention deficit hyperactivity disorder: associations with comorbid aggression and explanatory attributional mechanisms. *J Abnorm Child Psychol.* 2001;29:23-39.
14. Chambers WJ, Puig-Antich J, Hirsch M, et al. The assessment of affective disorders in children and adolescents by semistructured interview. Test-retest reliability of the schedule for affective disorders and schizophrenia for school-age children, present episode version. *Arch Gen Psychiatry.* 1985;42:696-702.

小児のトウレット障害(2)その併存症

金　生　由紀子*

Key words：tics, Tourette's disorder, comorbidity, obsessive-compulsive disorder: OCD, attention-deficit/hyperactivity disorder: AD/HD

要旨：トウレット障害は多様な併存症をしばしば有することが特徴の一つである．チックよりも併存症の方が社会的機能の妨げとなることも少なくない．併存症の中でも強迫性障害(obsessive-compulsive disorder: OCD)，注意欠如/多動性障害(attention-deficit/hyperactivity disorder: AD/HD)が特に高率である．また，トウレット障害を特徴づける強迫性と衝動性を有する併存症としては，"怒り発作(rage attack)"，広汎性発達障害(pervasive developmental disorders: PDD)も見逃せない．ここでは，上記の4つを中心に併存症を有するトウレット障害患者の特徴を概説して，トウレット障害の治療にあたっては併存症も含めて患者全体を総合的に理解することが重要であると指摘した．

Ⅰ．はじめに

トウレット障害は，チックで定義される症候群であるが，臨床で出会う患者では併存症を伴っている場合が少なくない．併存症の方を主訴にして受診をしたが，経過中にトウレット障害でもあると判明することがある．そして，治療の主な標的はその後も併存症であったとしても，トウレット障害の診断がついたことで，患者全体の理解が深まりより適切な治療が行えるようになると思われる．ここではトウレット障害の併存症の広がりに触れてから，小児の臨床でしばしば問題になる4つの併存症を取り上げて自らのデータを交えて述べたい．

Ⅱ．トウレット障害における併存症

トウレット障害患者では併存症を持たない割合は約10%しかないとの報告もあるほどであり(Freemanら，2007; Mol Debesら，2008)，さまざまな併存症を認めるが，その中でも強迫性障害(obsessive-compulsive disorder: OCD)および注意欠如多動性障害(attention-deficit/hyperactivity disorder: AD/HD)が特に高率とされる(図1)．また，習癖異常や強迫スペクトラム障害(obsessive-compulsive spectrum disorders)に含まれる疾患もしばしば併存する．

習癖は，狭義では身体をいじる癖(身体玩弄癖：指しゃぶり，爪かみ，抜毛癖，自慰など)を

Yukiko KANO: Comorbidities in Pediatric Patients with Tourette's Disorder
*東京大学医学部附属病院「こころの発達」診療部［〒113–8655 東京都文京区本郷7–3–1］

高率に併存する疾患

- 強迫性障害（obsessive-compulsive disorder: OCD）
- 注意欠如 / 多動性障害（attention-deficit/hyperactivity disorder: AD/HD）
- 学習障害（learning disabilities: LD）

習癖異常や強迫スペクトラム障害に含まれる疾患

- 吃音症
- 抜毛症
- 身体醜形障害
- 摂食障害
- 広汎性発達障害（pervasive developmental disorders: PDD）

その他の疾患，症状

- 分離不安障害
- パニック障害
- その他の不安障害
- 気分障害
- 睡眠障害
- "怒り発作"

図1　トウレット障害の併存症の広がり

指すが，広義では身体の動きを伴う癖，さらには睡眠(夢中遊行，夜驚症など)，言語(吃音，緘黙など)，食事(食思不振，過食，異食など)，排泄(遺尿症，遺糞症など)などの日常生活上の癖までも含むことがある．習癖は，心理的葛藤によるとかつては考えられていたが，現在では，神経系の発達に対応した好発年齢があることや素因がしばしば関与することなどから必ずしも心理的葛藤によるものではないと理解されており，チックと共通している(金生，2007)．

強迫スペクトラム障害とは，OCDとの間で，思考や行動を反復するという現象の類似，相互に併発しやすいこと，神経生物学的所見の類似(前頭葉や基底核などの機能の異常)，治療反応性の類似(セロトニン再取り込み阻害薬で軽快すること)などを認める疾患をまとめる概念である(金生，2007)．その範囲は報告によって若干異なるが，少なくともトウレット障害は必ず含まれている．

Ⅲ．OCDおよび強迫症状

OCDは，強迫観念または強迫行為を有して強い苦痛や社会的機能の著しい障害を生じている場合に診断される(表1)．OCDの小児患者では，成人患者と比べて強迫行為が強迫観念より優位であり，他者を巻き込みやすいという特徴があるが，強迫症状の種類は成人患者と大きく異ならず，強迫観念としては汚染に関するものが最も高率であり(表2)，強迫行為としては洗浄に関するものが最も高率である(表3)（Swedoら，1989; 金生，2002)．

トウレット障害ではOCDの併存率が約30％とされる．強迫症状を有するがOCDの診断基準を満たさない場合まで含めると過半数に及ぶ．

トウレット障害に特徴的な感覚症状に"まさにぴったり(just right)"感覚があり，OCDや強迫症状との親和性が高い．これは文字通り"まさにぴったり"とするまで行為をしなくてはならないという感覚である．トウレット障害患者134名(9～71歳)で調査したところ，OCDを併存する31名では81％，OCDではないが強迫症状を有する61名では56％に認められたという(Leckmanら，1994)．この感覚は強迫的な行動またはそれに続く行動についての視覚的または触覚的なものが主とされ，例えば，コップを机に置く際にコップの底が机の表面に"まさにぴったり"していると体感するまで何回も置きなおすことなどがある．

また，トウレット障害では，身体知覚(bodily sensations)と精神知覚(mental sensations)を含めた知覚現象(sensory phenomena)が特徴的との指摘もある．身体知覚は，患者が反復的行動を行う前に体の一部または全身に起こり，ムズムズとかチクチクなどと表現される感覚である．精神知覚には，反復行動を行おうという衝動(urge only)，内的な緊張または圧力が全般的に高まってきているという感覚(energy release)，完全ではないとか完璧ではないとか不十分であるという内的な感覚(incompleteness)が含まれる．先述した"まさにぴったり"感覚もその一つとされる．

表1　強迫性障害(Obsessive-compulsive disorder)の診断基準(DSM-IV-TR)

A. 強迫観念または強迫行為のどちらか.

(1), (2), (3), および(4)によって定義される強迫観念：

(1)反復的，持続的な思考，衝動，または心像であり，それは障害の期間の一時期には，侵入的で不適切なものとして体験されており，強い不安や苦痛を引き起こすことがある.

(2)その思考，衝動または心像は，単に現実生活の問題についての過剰な心配ではない.

(3)その人は，この思考，衝動，または心像を無視したり抑制したり，または何か他の思考または行為によって中和しようと試みる.

(4)その人は，その強迫的な思考，衝動または心像が(思考吹入の場合のように外部から強制されたものではなく)自分自身の心の産物であると認識している.

(1)および(2)によって定義される強迫行為：

(1)反復行動(例：手を洗う，順番に並べる，確認する)または心の中の行為(例：祈る，数を数える，声を出さずに言葉を繰り返す)であり，その人は強迫観念に反応して，または厳密に適用しなくてはならない規則に従って，それを行うよう駆り立てられていると感じている.

(2)その行動や心の中の行為は，苦痛を予防したり，緩和したり，または何か恐ろしい出来事や状況を避けることを目的としている．しかし，この行動や心の中の行為は，それによって中和したり予防したりしようとしていることとは現実的関連をもっていないし，または明らかに過剰である.

B. この障害の経過のある時点で，その人は，その強迫観念または強迫行為が過剰である，または不合理であると認識したことがある.

注：これは子供には適用されない.

C. 強迫観念または強迫行為は，強い苦痛を生じ，時間を浪費させ(1日1時間以上かかる)．またはその人の正常な毎日の生活習慣，職業(または学業)機能，または日常の社会的活動，他者との人間関係を著明に障害している.

D. 他のI軸の障害が存在している場合，強迫観念または強迫行為の内容がそれに限定されていない(例：摂食障害が存在する場合の食物へのとらわれ，抜毛癖が存在している場合の抜毛，身体醜形障害が存在している場合の外見についての心配，物質使用障害が存在している場合の薬物へのとらわれ，心気症が存在している場合の重篤な病気にかかっているというとらわれ，性嗜好異常が存在している場合の性的な衝動または空想へのとらわれ，または大うつ病性障害が存在している場合の罪悪感への反復思考).

E. その障害は，物質(例：乱用薬物，投薬)または一般身体疾患の直接的な生理学的作用によるものではない.

＊該当すれば特定せよ

洞察に乏しいもの　現在のエピソードのほとんどの期間，その人はその強迫観念および強迫行為が過剰であり，または不合理であることを認識していない.

さらに，チック的強迫症状とも呼べそうな衝動(impulsion)もトウレット障害に特徴的である．反復的に物を触ったり自分をたたいたりする行動がその典型であろう．複雑チックとされるコプロラリアやエコラリアも衝動に含まれるという．やってはいけないと思ってもとまらないというよりは，やってはいけないと思えば思うほどやってしまうという色彩が強く，強迫的であると同時にまさに衝動の統制に問題があると示す症状である(金生，印刷中).

知覚現象や衝動の頻度は，OCDの併存の有無にかかわらずトウレット障害であればOCDのみの場合よりも高率である．ただし，衝動の重症度は，トウレット障害とOCDを併存する場合にトウレット障害のみよりも強い．すなわち，OCDを併存したトウレット障害では，コプロラリアや自傷行為がより起こりやすく，チックがより重症になる可能性があると言えよう(金生，2006)．わが国の複数の医療機関から得られたトウレット障害患者のデータからも，強迫症状を

表2　OCDの小児・青年70名の主な強迫観念

・ごみ，細菌，環境の毒素の心配	40%
・何か恐ろしいこと(火事，自分が愛する人の死や病気など)が起こるのではないかという恐れ	24%
・対称，順序，厳密	17%
・几帳面さ(宗教的強迫観念)	13%
・身体の排泄物や分泌物(尿，便，唾液)の心配や嫌悪	8%
・幸運か不運の数字	8%
・許されない，攻撃的で，邪悪な性的考え，イメージ，衝動	4%
・他人か自分を傷つけてしまうのではないかという恐れ	4%
・家庭内の物の心配	3%
・侵入してくる無意味な音，言葉，音楽	1%

(Swedoら，1989)より

表3　OCDの小児・青年70名の主な強迫行為

・過度な儀式的な手洗い，シャワー，入浴，歯磨き，身繕い	85%
・反復する儀式(ドアから出たり入ったりする，椅子から立ったり座ったりするなど)	51%
・確認(ドア，錠，コンロ，電気器具，車の非常ブレーキなど)	46%
・汚れとの接触を取り除こうとする儀式	23%
・触ること	20%
・数えること	18%
・配列，整頓	17%
・自分や他人を傷つけるのを避けるための処置	16%
・貯蔵，収集の儀式	11%
・家財道具や生命のない物を掃除する儀式	6%
・種々の儀式(例えば，書く，動く，話す)	26%

(Swedoら，1989)より

併存するトウレット障害では自傷行為がより高率で，チック自体やチックによる悪影響がより重症であることが示唆された(表4)．

トウレット障害の経過では，チックは小学校高学年から高校の初め頃までに最悪時を迎えて以降は軽快に転じることが多いが，むしろそれと入れ替わるように強迫症状が問題になってくることも少なくない．

Ⅳ．注意欠如/多動性障害(Attention-deficit/hyperactivity disorder: AD/HD)

AD/HDはトウレット障害の併存症の中で，OCDと並んでその頻度が高く50%以上にも及ぶと報告されている．

ただし，チックの発症後にAD/HDの特徴が目立ってきたという場合には，チックの動きが多動と誤解されている可能性もある．また，チックをやらずにはいられないという抵抗しがたい感覚(前駆衝動: premonitory urges)を含めてチックに密接にかかわる落ち着きのなさの問題が大きいかもしれない．AD/HDの患者にトウレット障害が発症してくる場合と，トウレット障害の患者でチックの発症や増悪に伴ってAD/HD症状が目立ってくる場合とでは，本態が異なる場合もあると思われる(Greimelら，2008)．

AD/HDを伴うと，チック自体が重症になるわけではないが，衝動性や攻撃性が増加し，生活に支障をきたす．また，AD/HDを伴った場合には，当然かもしれないが，学習障害や協調性発達運動障害というAD/HDに親和性の高い疾患を伴う率も高まる(表4，表5)．さらに，怒りの問題や自傷行為も起こしやすいとの指摘もある(Freemanら，2007)．

トウレット障害小児患者314名について併存症を体系的に調査して，AD/HDおよび/またはOCDを伴う場合には，怒り，季節性気分障害の症状，睡眠障害，抑うつ病状を有する割合が，それらを伴わない場合よりも有意に高かったとの報告がある(Mol Debesら，2008)．この調査では，AD/HDとOCDの両方を伴う場合にチックが最も重症であったという．また，トウレット障害の222家族の成員(発端者，両親，同胞)952名のデータを潜在クラス分析をしたところ5

表4　併存症による3群比較

	TD+HD (n = 15)	TD+OCS (n = 27)	TD only (n = 36)	統計
平均年齢	11.9 (SD: 2.5)	20.7 (SD: 0.1)	13.0 (SD: 4.0)	p = 0.000
チック以外の臨床特徴				
衝動性 / 攻撃性	6 (40.0%)	14 (53.8%)	3 (8.3%)	p = 0.000
不登校	4 (26.7%)	12 (44.4%)	5 (14.3%)	p = 0.030
自傷行為	1 (7.1%)	10 (37.0%)	1 (2.9%)	p = 0.001
不器用	6 (40.0%)	2 (7.4%)	1 (2.8%)	p = 0.001
学習障害	6 (42.9%)	0 (0.0%)	1 (2.9%)	p = 0.000
臨床家による5段階評価で最悪時に"重度"または"最重度"				
チック症状全体	9 (64.3%)	22 (88.0%)	17 (47.2%)	p = 0.005
チックによる悪影響	7 (53.8%)	19 (70.4%)	9 (25.0%)	p = 0.001
全体的な適応の障害	6 (40.0%)	16 (59.3%)	3 (8.3%)	p = 0.000

TD+HD: TD + 多動性障害 (HD)　　TD+OCS: TD + 強迫症状 (OCS)
TD only: 併存症を伴わないTD
統計: 平均年齢についてはt-検定，その他は χ^2-検定

表5　AD/HDの併存と他の併存症および薬物療法
(国際データーベース研究から)

	TD+AD/HD (n = 3,783)	TD-AD/HD (n = 2,055)	2群間の統計量	TDのみ (n = 967)
気分障害	14%	8%	p<0.001	該当せず
特異的学習障害	33%	12%	p<0.001	該当せず
発達性協調運動障害	14%	7%	p<0.001	該当せず
怒り	39%	16%	p<0.001	9.0%
自傷行為	14%	9%	p<0.001	3.5%
チックへの薬物療法	54%	43%	p<0.001	35%

各群の人数は小児と成人の合計．
表中のパーセントは各群の小児に占める割合．

(Freemanら, 2007)より

群に分かれて，トウレット障害＋AD/HD＋OCDの群のみが遺伝性が高かったとの報告もある(Gradosら，2008)．AD/HDとOCDの両方を併存するトウレット障害患者は特有な一群であるかもしれない．

トウレット障害とAD/HDとの併発では，チック以上にAD/HDに伴う行動症状が問題となることも多く，それに対しては中枢刺激薬の効果が期待される．AD/HDに中枢刺激薬を使用するとチックの誘発や増悪をきたす恐れがあると以前にはしばしば指摘されたが，最近では危険性よりも利益の方が大きいとの報告が複数ある．その中でも有力なものが，AD/HDと慢性チック障害を有する小児患者136名を，cloni-

dineの み，methylphenidateの み，clonidine + methylphenidate，プラセボの4群に無作為割付けした多施設協同の二重盲検試験である(Tourette's Syndrome Study Group，2002)．初めの4週間はclonidineまたはプラセボを，次の4週間はmethylphenidateまたはプラセボを服用し，その後8週間は維持療法とした．プラセボと比べて最も有効であったのはclonidine + methylphenidateであった．clonidineは衝動性及び多動性に有効であり，methylphenidateは不注意に有効であった．副作用としてチックを報告した割合はmethylphenidateで20％であり，clonidineのみ(26％)やプラセボ(22％)に比べて高くなかった．このような大規模研究で安全性が確認されたにもかかわらず，わが国ではmethylphenidate徐放薬の認可にあたって，チックを誘発や増悪させるとして，「運動性チックのある患者，Tourette症候群またはその既往歴・家族歴のある患者」には禁忌となっている．中枢刺激薬の代わりとしてはノルアドレナリン系への作用が強い抗うつ薬が考えられる．現在治験中であるatomoxetineが使用可能となれば有力な選択肢となろう．

V．“怒り発作(rage attack)”

“怒り発作”とは，状況にはとても過度または不適切にひどく腹を立ててコントロールできなくなることである．言葉による攻撃あるいは暴言，器物への物理的な攻撃，他人への身体的な攻撃を含む．トウレット障害の小児患者はたいてい素直でやさしいのだが，その元来の性格には似つかわしくない行動であり，まさに“きれる”という表現がぴったりである．

トウレット障害の小児・青年患者29名で“怒り発作”に重点を置いて過去1カ月について攻撃性を0（なし：攻撃性はないか，あっても適応に影響しない）から4（最重度：攻撃性が非常に目立ち，日常生活が困難である）の5段階で評価したところ，攻撃性が1以上で有りとした場合に，自傷行為が有意に高率であり，チックが重症な傾向を認めた(Kanoら，2008)．“怒り発作”を併存するトウレット障害患者には，AD/HD，OCD，反抗挑戦性障害を併存することが多いとの報告があるが(Budmanら，2000)，この対象では攻撃性の有無で併存症に差はなかった．この29名の中でChild Behavior Checklist（CBCL）による評価が得られた23名について攻撃性の有無で比較すると，攻撃性有りの場合には，8つの下位尺度の中で攻撃的行動に加えて，不安/抑うつ，思考の問題が有意に高得点であった．思考の問題には強迫症状に該当する項目が複数あることから，自分のイメージどおりにいかないと気がすまない傾向が基盤にあってそれが適わないと“怒り発作”につながる可能性もあるのではと思われる．また，“怒り発作”を示すトウレット障害患者では，攻撃性のみに目を奪われずに自己評価の低下にも配慮が要ると考えられる．

VI．広汎性発達障害(Pervasive developmental disorders: PDD)

トウレット障害患者にPDDを併存する頻度は1％～9％と報告されている．一方で，PDD患者にトウレット障害を併存する頻度は2.6％～50％と報告による違いが大きいが，いずれにしてもPDDでは一般人口より高い頻度でトウレット障害を認めると言えよう(桑原ら，2006)．

トウレット障害とPDDとの併存は知的な遅れの有無や程度にかかわらず起こる．PDD患者にトウレット障害が発症しても発達が促進されることはなく，トウレット障害を伴わないPDD患者と比べて強迫性と衝動性が高まり自傷や他害などの攻撃行動を生じやすくなり，適応が悪くなる．

典型的なトウレット障害患者は社交的であり周囲へ気を使う傾向が強くて気持ちの表現も上手なことが多く，自閉症の3主徴に含まれる対人的相互反応の質的障害およびコミュニケーションの質的障害に該当する特徴は認め難い．しかし，残る一つの自閉症の主徴である行動，興味および活動の限定され，反復的で常同的な様式については，トウレット障害とPDDとで共通性が高いと思われる．すなわち，どちらも，やってはいけないと思えば思うほどやってしまうという衝動性の高さで特徴付けられる強迫様症状を有している(金生，2008)．

自験例で自閉症またはアスペルガー障害が確診できず知的な遅れを伴わないトウレット障害患者44名について詳細な評価を行ったところ，最終的に4名がPDDであると判明した．トウレット障害患者にPDDを併存する頻度は9.1%となった．この4名の患者と同時期に外来通院中であり，知的な遅れはないものの当初から自閉症またはアスペルガー障害と診断されていたため対象から除外された患者が6名いたので，それらを加えて，トウレット障害とPDDとの併存患者10名について検討した．PDDを伴わないトウレット障害患者40名と比較して，チックの種類，AD/HD症状や自傷行為の頻度などに大差はなかった．しかし，OCDを併存する割合は，PDDを伴う場合に60%であるのに対して，PDDを伴わない場合に20%であり，トウレット障害とPDDとの併存患者で有意に高率であった．しかもOCDと診断された患者全員が，強迫症状が過剰である，または不合理であると認識したことがあり，自閉症のこだわりとは明らかに異なる典型的な強迫症状を有していた．トウレット障害とPDDが強迫性を共有すると改めて確認されたと言えよう．また，詳細な評価の後にPDDの併存が確定した4名は，チックが比較的重症であり，OCDまたは強迫症状を併存しており，さらに，意欲減退，注意散漫，睡眠障害，不登校などの行動上の問題を伴っていた．薬物療法などによってチックが軽減して活動性も高まるにつれて，相手の気持ちや場に合わせた言動がとれないことが明らかとなり，不適応の基盤にPDDが存在することが浮き上がってきたと思われる．

このトウレット障害とPDDとの併存患者10名は，チックの発症年齢の平均が約7歳であり，トウレット障害としては標準的であった．チックのための最初の医療機関受診年齢の平均が約10歳であると同時に，PDDに気づかれた年齢の平均も約10歳であり，チックに加えて対人関係などの問題が目立ってきてついに受診になった可能性があると思われた．不登校は60%と高率であり，トウレット障害とPDDとの併存が学校での適応に与える影響の大きさがうかがえた．同時に，50%が通級学級や適応指導教室の利用を含めた特別な教育的支援を受けていた．

Ⅶ．治療から見た併存症

治療のためにはトウレット障害患者を総合的に評価することが重要である．トウレット障害の重症度としては，チックの頻度，強さ，複雑さ，行動や発語への影響などからなるチック自体の重症度，自己評価や社会的機能に対するチックの直接的な悪影響の重症度を把握する必要がある．同時に，これまで述べてきたような併存症の有無および重症度を考慮する必要がある．併存症のない場合もあるが，複数の併存症を有する場合も少なくないだろう．チックとすべての併存症を見渡して治療の優先順位をつけていくことになる．

治療の優先順位を考える上では，患者本人および周囲の受けとめ方を把握することも重要である．例えば，患者は極めて頻回の瞬目チックがうっとおしくて気になっているのに対して，