Intermittent explosive disorder in adults: Epidemiology and pathogenesis

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INTRODUCTION

Patients with intermittent explosive disorder have impulsive, aggressive verbal outbursts at least twice a week and serious, physically assaultive behavior at least three times a year [1-3]. The aggressive behaviors are unplanned, out of proportion to the provocation, and cause subjective distress or psychosocial impairment.

This topic reviews the epidemiology and pathogenesis of intermittent explosive disorder. The clinical features, assessment, diagnosis, treatment, and prognosis are discussed separately. (See "Intermittent explosive disorder in adults: Clinical features, assessment, and diagnosis" and "Intermittent explosive disorder in adults: Treatment and prognosis".)

EPIDEMIOLOGY

Estimates of the lifetime prevalence of intermittent explosive disorder range from 1 to 7 percent, depending upon the study population [4,5]. However, the prevalence of intermittent explosive disorder is not well established because most studies [5] relied upon diagnostic criteria from the American Psychiatric Association's Diagnostic and Statistical Manual, Fourth Edition (DSM-IV) [6], rather than the more recent Diagnostic and Statistical Manual, Fifth Edition (DSM-5) [3]. The DSM-IV criteria had several limitations, such as not requiring that the aggressive behavior be impulsive rather than planned, not providing operationalized criteria on

the nature and frequency of impulsive aggressive behavior, and not clearly specifying exclusionary disorders [2,7].

General population — Using various diagnostic criteria, nationally representative surveys of the general adult population in different countries estimate that the lifetime prevalence of intermittent explosive disorder is 1 to 4 percent (table 1) [8-12]. The estimated 12-month prevalence ranges from 1 to 3 percent [8,9,11-14].

A survey in the United States, using diagnostic criteria from DSM-5 [3], found that the lifetime prevalence of intermittent explosive disorder was approximately 4 percent and the past-year prevalence was close to 3 percent [15]. The survey also found that the lifetime and past-year prevalence of serious, physically assaultive behavior at least three times a year (one of the DSM-5 criteria) was approximately 8 and 6 percent [16].

The DSM-5 diagnostic criteria for intermittent explosive disorder are discussed separately. (See "Intermittent explosive disorder in adults: Clinical features, assessment, and diagnosis", section on 'Diagnosis'.)

Sociodemographic correlates — Onset of intermittent explosive disorder often occurs at an early age. In a cross-national study of community surveys from 16 countries, the median age of onset was 17 years; in the United States, the median age of onset was 14 years [5].

Community surveys show that the disorder occurs more often in males and younger individuals (eg, age <60 years) [5]. In addition, the disorder is modestly associated with being divorced or separated, unemployed, and not finishing college.

Clinical settings — The estimated lifetime prevalence of intermittent explosive disorder in psychiatric patients is 6 to 7 percent, and the point (current) prevalence is 3 to 6 percent:

- A study of 1300 outpatients found that the lifetime prevalence of intermittent explosive disorder was 6 percent, and the point prevalence was 3 percent [17].
- A study of 204 inpatients found that the lifetime prevalence of intermittent explosive disorder was 7 percent, and the point prevalence was 6 percent [4].

PATHOGENESIS

The pathogenesis of intermittent explosive disorder is not known. Many authorities think that the etiology involves biologic, psychological, and social factors [18].

Genetics — There is probably a genetic component to intermittent explosive disorder [19-22]. A study using blinded raters found a positive family history of intermittent explosive disorder in more first-degree relatives (parents, siblings, or offspring) of patients with the disorder (n = 32) than in relatives of nonaggressive controls (n = 32; 34 versus 10 percent) [23]. In addition, twin and family studies suggest that 44 to 72 percent of the likelihood of developing impulsive aggressive behavior is genetic [18]. This is consistent with a meta-analysis of 24 twin and adoption studies of aggression (number of subjects not specified), which found that genetic factors accounted for approximately 50 percent of the variance in aggression [24].

Neurobiology — Multiple lines of evidence demonstrate that brain structure and function are altered in intermittent explosive disorder. As an example, structural, functional, and connectivity brain magnetic resonance imaging studies suggest that the amygdala, which is involved in emotional functioning, is affected. However, it is not clear whether the observed abnormalities represent etiologic causes, sequelae, neither, or both.

Neuroimaging — Impulsive, aggressive behavior has been conceptualized as an imbalance between excessive, aggressive drives originating in limbic brain structures such as the amygdala, and insufficient control of these impulses by cortical structures such as the orbital frontal cortex and anterior cingulate cortex [18]. Support for this hypothesis includes functional magnetic resonance imaging studies that presented photographs of angry faces to patients with intermittent explosive disorder and healthy controls [25,26]. Compared with controls, patients exhibited increased activation of the amygdala and reduced activation of the orbitofrontal cortex. However, this finding may be present only in the context of social threat [27].

Other brain magnetic resonance imaging studies in patients with intermittent explosive disorder have also found abnormalities in the amygdala, as well as other areas:

- Structural imaging of 67 individuals with intermittent explosive disorder and 73 healthy controls found that intermittent explosive disorder was associated with greater localized, inwardly directed deformations in the shape of the amygdala and hippocampus [28]. The deformations suggested loss of neurons.

- Structural imaging found that the volume of the amygdala and other gray matter structures (eg, orbitofrontal cortex and anterior cingulate cortex) was smaller in individuals with intermittent explosive disorder (n = 57), compared with healthy controls (n = 53) and with individuals with other psychiatric disorders (eg, depressive or anxiety disorders; n = 58) [29]. In addition, frontal-limbic gray matter volume across all subjects was inversely related to aggressive behavior and tendencies.

- Connectivity imaging found that integrity of white matter tracts between the frontal and temporoparietal regions was reduced in intermittent explosive disorder (n = 42), compared with healthy controls (n = 40) and psychiatric controls (n = 50) [30].

Serotonergic activity — On a molecular level, multiple studies suggest that serotonergic activity in patients with intermittent explosive disorder is reduced [2,31]. As an example:

- A study examined the number of platelet serotonin binding sites as a proxy for central nervous system serotonin activity and found fewer binding sites in 35 patients with intermittent explosive disorder, compared with 65 controls [32].

- A study found that response to a single dose of the serotonin releasing agent dexfenfluramine was significantly reduced in 62 patients with intermittent explosive disorder, compared with 38 controls [33].

- One positron emission tomography study found less serotonergic innervation in the anterior cingulate cortex in 10 patients with intermittent explosive disorder, compared with 10 healthy controls [34]. While a second larger study (n = 29 patients and 30 controls) did not replicate this finding, the second study reported an inverse relationship between state aggression levels and serotonin transporter availability in subcortical regions (striatum and thalamus) [35].

Inflammation — Serum inflammatory proteins appear to be elevated in patients with intermittent explosive disorder. A study compared C-reactive protein and interleukin 6 levels in patients with intermittent explosive disorder (n = 69), healthy controls (n = 67), and nonaggressive patients with other psychiatric disorders (n = 61); all subjects were physically healthy, and the analyses controlled for several potential confounding factors (age, body mass index, depression, and psychological stress) [36]. Levels of both inflammatory markers were higher in patients with intermittent explosive disorder compared with healthy and psychiatric controls, and were directly correlated with a composite measure of aggression. This was not due to differences in tryptophan-kynurenine pathway metabolites [37].

In an overlapping group of study participants, individuals with intermittent explosive disorder displayed increased concentrations of serum markers of oxidative stress, compared with healthy controls and with psychiatric controls [38]. Oxidative stress, which is an inherent part of inflammation, could account for possible cellular damage in the central nervous system (eg, reduced gray matter).

A subsequent study of gene expression included patients with intermittent explosive disorder (n = 45) and both psychiatric and healthy controls (n = 79) [39]. The results found that intermittent

explosive disorder has a distinct immunoregulatory profile, including upregulated activity for antiviral response, suggesting that its etiology may involve a pathogen-driven immune response.

Infection — Infection with *Toxoplasma gondii*, which can localize in brain tissue, may be associated with intermittent explosive disorder. One study found that seropositivity to *Toxoplasma gondii* antibodies occurred in more individuals with a lifetime diagnosis of intermittent explosive disorder (n = 110) than healthy controls (n = 110; 22 versus 9 percent) [40]. In addition, aggressive behavior and tendencies, as assessed across all subjects, were greater in seropositive individuals than seronegative individuals.

Psychosocial factors — Family environment and exposure to multiple traumas (eg, physical abuse and witnessing family violence as a child) may be involved in the pathogenesis of intermittent explosive disorder [18]:

- A cross-national study of community surveys from 16 countries found that after controlling for potential confounding factors (eg, age, sex, and country), onset of intermittent explosive disorder was more than twice as likely among individuals with a prior, childhood history of physical abuse or witnessing family violence [5]. In addition, the association between trauma and subsequent onset of intermittent explosive disorder became larger as individuals suffered an increasing number of different types of trauma.

- A retrospective study found that a history of sexual abuse, physical abuse or neglect, or emotional abuse or neglect was more extensive in patients with a lifetime history of intermittent explosive disorder (n = 264) than patients with other psychiatric disorders (n = 199) and healthy controls (n = 185) [41].

SUMMARY

- Intermittent explosive disorder is characterized by recurrent, impulsive aggressive behavior that is distinguished from both premeditated aggression as well as defensive aggression provoked by an immediate threat. (See "Intermittent explosive disorder in adults: Clinical features, assessment, and diagnosis", section on 'Aggression'.)

- General population surveys estimate that the lifetime prevalence of intermittent explosive disorder is 1 to 4 percent (table 1); the prevalence in clinical settings is 6 to 7 percent. The median age of onset is approximately 17 years, and the disorder occurs more often in males and individuals aged less than 60 years. (See 'Epidemiology' above.)

- Although the pathogenesis of intermittent explosive disorder is not known, there appears to be a genetic component. In addition, structural, functional, and connectivity brain magnetic resonance imaging studies suggest that the amygdala and other brain areas are involved. (See 'Pathogenesis' above.)

- Several treatments are available for intermittent explosive disorder. (See "Intermittent explosive disorder in adults: Treatment and prognosis".)

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