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ORIGINAL PAPER

Generalized Anxiety Disorder: Revisited

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Abstract
Generalized Anxiety Disorder (GAD) from an official recognition as a residual category in DSM-III has come a long way to be appreciated as a common underlying anxiety pathway in the literature. Despite still being defined as extreme anxiety and worry upon performance and about one's health, GAD seems to be a general umbrella of anxiety, covering even social anxiety and panic disorder (PD) and even when not treated and chronic, leading to major depressive disorder (MDD). Along the line of some other similar studies and contentions, in the present study we sought to validate the hypothesis of GAD encompassing social anxiety as well as performance anxiety and its extension to PD and MDD. We also examined the onset of each diagnostic category of GAD, PD and MDD and their developmental course in our clinical sample. 113 patients with Generalized Anxiety Disorder (GAD) out of 295 referrals to our mood and anxiety clinic during the three months of May–July 2019, were identified and included in this research. We expanded the definition of GAD as per our clinical observation to include any situations triggering the anxiety including any performance and social situations and did not exclude if the anxiety led to panic attacks. The results of our study showed that an encompassing GAD (including performance and social anxiety) has an early onset, recognized partially in childhood, but mostly during adolescence. An untreated GAD was complicated with panic disorder and episodes of major depression, each with an onset later in life. GAD in our study was also found to be familial and genetic, while its post-morbid depression seemed to be more a reaction to a long-standing untreated anxiety. The findings of our study if replicated has research implication of better understanding the developmental course of mood disorders and hold the promise of more targeted treatments of anxiety, panic and depression in clinical practice.

Keywords Generalized anxiety disorder · GAD · Social anxiety · Panic attacks · Panic disorder · Post-morbid depression

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Introduction

Generalized Anxiety Disorder (GAD) is one of the oldest psychiatric disorders known to man, even back to antiquity and recorded by the father of medicine, Hippocrates [1]. GAD that was introduced in the third edition of the Diagnostic and Statistical Manual (DSM-III) in 1980 [2] was only a residual category that could be diagnosed if no other anxiety disorders were present. Soon GAD started to have its own diagnostic criteria as a separate mood disorder entity in the following editions of the manual up to the current DSM5 [3]. GAD has been defined by DSM5 with no major change from its earlier edition in the DSM-IV. GAD is described (Table 1) basically as having excessive anxiety and worry (apprehensive expectation), difficulty to control the worry, and association of the anxiety and worry with three (or more) of physical and cognitive symptoms of restlessness, feeling keyed up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, and sleep disturbance.

The validity of GAD and its exact symptom inclusion have been questioned by some (e.g. [4, 5]). It has been shown as early as 1986 that GAD as being more chronic than panic disorder, with more generalized and primary symptoms present in almost all other anxiety disorders with the exception of simple phobia [6]. Others have argued that GAD could be a common anxiety disorder pathway leading to other mood disorders such as panic disorder (PD) and even major depression. For example, in epidemiological studies, PD has been the most highly comorbid with GAD ranging from 55 to 94% [7, 8]. Among all anxiety disorders, only adult PD and GAD respectively have predicted each other over a 3-year period [9]. Significant percentages of PD patients have also been shown to meet the GAD criteria before their first panic attacks [10].

Developmental course studies from childhood to adolescence and adulthood have also shown the overlap and extension of anxiety disorders, e.g. a Norwegian clinical cohort that has shown social anxiety predicts later GAD [11]. A Dutch study of 10- to 12-year-old suffering from separation, social anxiety and panic disorders also has showed that high scores on one anxiety dimension implicated high scores on the other anxiety dimensions [12]. Also, childhood depression, social phobia, and Post Traumatic Stress Disorder (PTSD) have been shown to be associated with adult GAD, and higher levels of maternal insecure avoidant attachment has been more predictive of GAD relative to PD [13].

Table 1 DSM5 generalized anxiety disorder diagnostic criteria

A.	Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance).
B.	The individual finds it difficult to control the worry.
C.	The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms having been present for more days than not for the past 6 months): Note: Only one item required in children. 1. Restlessness, feeling keyed up or on edge.2. Being easily fatigued.3. Difficulty concentrating or mind going blank.4. Irritability.5. Muscle tension.6. Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep).
D.	The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
E.	The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hyperthyroidism).
F.	The disturbance is not better explained by another medical disorder (e.g., anxiety or worry about having panic attacks in panic disorder, negative evaluation in social anxiety disorder [social phobia], contamination or other obsessions in obsessive-compulsive disorder, separation from attachment figures in separation anxiety disorder, reminders of traumatic events in posttraumatic stress disorder, gaining weight in anorexia nervosa, physical complaints in somatic symptom disorder, perceived appearance flaws in body dysmorphic disorder, having a serious illness in illness anxiety disorder, or the content of delusional beliefs in schizophrenia or delusional disorder).

In the present study we sought to determine if the anxiety and worry consistent with GAD is triggered upon performance and/or in relation to one's health could arise in social situations and also upon escalation leading to panic attacks (or disorder), and if prolonged untreated GAD would also lead to major depressive disorder (MDD). We also explored the age of onset of GAD and any of its post-morbid events of PD and MDD.

Method

Of 295 referrals to our mood and anxiety clinic for assessment and treatment during the three months of May–July 2019, we identified and diagnosed 113 cases (62 females and 51 males) with excessive anxiety and worry lasting more than 6 months meeting the DSM5 criteria of GAD. The assessments were done by clinical interviews asking the questions in Table 2. We included any situations that trigger the anxiety including any performance such as in school upon tests, exams, presentations, interviews or even competitions such as sports. We did not exclude the social situations that could trigger anxiety, with or without avoidance of the situations(social phobia). We also included anxiety and worry alone without any triggers. The questions also included if the anxiety and worry lead to anxiety or panic attacks, not worry about having panic attacks to distinguish it from panic disorder. In addition to including the minimum 6 months of suffering, we included dysfunctionality in social, occupational, or any other important areas of the individual's life. The questions also included if the anxiety has ever led to any depressive episode longer than 2 weeks to meet the DSM5 criteria for MDD. The age of onset of anxiety, panic attacks, depression, and the family history of anxiety were also identified.

Table 2 GAD questionnaire

1. Do you usually get excessively anxious, worried or stressed upon performance such as in school upon tests, exams, presentations, interviews or competitions?
2. Do you usually get excessively anxious, worried or stressed in social situations, crowds or with strangers?
3. Do you dislike and usually try to avoid anxiety provoking situations?
4. Are you a worrier and do you anticipate the worst of the situations?
5. Have you found difficult to control your anxiety and worries?
6. Are you usually restless or feeling keyed up or on edge?
7. Do you feel easily fatigued?
8. Do you usually have difficulty concentrating or experience your mind going blank?
9. Are you usually irritable?
10. Do you usually have muscle tension?
11. Do you usually have any sleep disturbances such as difficulty falling or staying asleep, or having restless, unsatisfying sleep?
12. Have you ever had any anxiety or panic attacks with uncomfortable physical symptoms such as rapid heart rate, sweating, shortness of breath, chest pain, dizziness, shakes?
13. Has your anxiety caused dysfunction in any parts of your social, occupational, or any other important parts of your life?
14. Have you ever had any episode of depression, lasting more than 2 weeks?
15. Has your depression been reactive to your stress, anxiety and situational?
16. When did you first experience your anxiety?
17. When did you first experience your depression?
18. Does anybody else in your family suffers from anxiety and worries?

Results

The age range of the sample was between 12 to 67 years old, consisted of 5 children (<13 years old) (5%), 15 adolescents (<19 years old) (14%), and 93 adults (29% in their 20s, 20% in their 30s, 19% in their 40s, 11% in their 50s, and 2% in their 60s). The performance anxiety was the highest form of anxiety with 74%, followed by social anxiety with 56%, and anxiety in both performance and social situations as 49% in our sample. Anxiety and worry about performance and/or social context such as worries about health of oneself and relatives or pure worriers were reported only in 4 subjects or 3.5% of our sample. Panic attacks were reported in 62% and major depression (>2 weeks) was reported in 86% of the sample. The onset of anxiety in childhood was reported in 16%, while during adolescence in 77% and only 7% in adulthood. The onset of any major depressive episode was reported as none during childhood, 19% during adolescence and 81% in adulthood (with 41% onset after the age of 30). The panic onset was reported as none during childhood, 49% during adolescence and 51% during adulthood, mostly in 20s (47%). The family history of anxiety was reported in 62% of the sample.

Discussion

GAD as an Underlying Anxiety Disorder

Our study along the line with some other developmental course studies of GAD [10–13].

showed that social anxiety could not be separated from GAD as more than half of our sample (56%) had this type of anxiety. Moreover panic disorder could not either be isolated as a stand-alone disease entity springing out of void, as that could be an escalation of anxiety in GAD as 62% of our sample had incidents of panic attacks. Major depression when mixed with anxiety could be also counted as an extension or complication of untreated GAD as most of our sample (86%) reported episodes of MDD.

DSM5 identifies that the anxiety and worry in GAD as "frequently occurs without precipitants", but admits to be related to "school and sporting performance" in children and adolescence and "well-being of family or their own physical health" [3]. Despite no precipitants needed for DSM to diagnose GAD, the diagnostic manual identifies the primary difference of the disorder "across age group is in the content of the individual's worry". While this content could be about performance in different areas and "impairment in social, occupational or other important areas of functioning" [3], still social anxiety is considered as a different disorder entity.

The anxiety and worry in our data occurs within a context, e.g. performance, social or heath concerns and is precipitated by such situations that may appear as significant or trivial in the eyes of others. Therefore, taking the context or precipitant out of the equation or diagnostic criteria would be like imagining a pure anxiety in void that might not exist in reality or being observed in clinical practice. Since many patients may have anxiety and worries in more than one context, e.g. performance and social (almost half of our sample, 49%) it would be more prudent not to divide GAD and classify social anxiety as a different disease entity. In fact, the term Generalized Anxiety Disorder could be more meaningful with the generalization of the anxiety being across contexts, ages and severity.

In addition since many patients with GAD end up having panic attacks (62% of our sample) it would be more reasonable to perceive the panic attacks or panic disorder as an extension and

complication of the severity of GAD and not as a separate disease entity. Lastly, since the majority of GAD subjects in over time develop major depression lasting over two weeks (86% in our data) it would be more realistic to perceive depression in GAD as a complication or consequence of chronicity and lack of treatment of this disorder. As it has been shown in other studies, the high degree of overlap among the anxiety disorders from childhood across the life span also indicates the high probability of a common pathophysiologic construct such as negative affectivity or temperament sensitivity which refutes the separation of many anxiety disorders into different diagnostic categories [14–18]. Longitudinal studies into the developmental course of anxiety disorders have shown beyond overlap within these disorders, but progression of one to another, mostly GAD to PD and MDD. The progression of one disorder to another namely "heterotypic continuity" has been reported among the different anxiety disorders and major depression [19, 20].

The comorbidity and high correlation of anxiety and depressive disorders up to 61.9% have been in discussion as early as 1992 by Brady and Kendall [21]. They identified the anxiety in a younger age predates the depressive symptoms later on, so they proposed a developmental sequence in progression of these mood disorders. Since the comorbidity of anxiety and depression has been studied by many and estimated to be as high as 75%, and the progression of anxiety in early life to depression in later life have been confirmed (e.g.22–24). Further studies have also shown that anxiety having an earlier age of onset is more prevalent in childhood than depression, while depression is more prevalent in adolescence, thus the degree of comorbidity may vary by age (e.g. 25–26).

The Age of Onset

Our results showed that GAD could have an onset as early as childhood in 16% of our sample with 5% of the total sample presented to our clinic during this young age period. The majority of anxiety in GAD if not recognized by the subject during childhood, was identified by adolescence (77%) and 14% of our total sample presented and sought medical help during their teens. The late onset of anxiety in adulthood was only in a minority (7%) of our sample. Our data seemed to be in contrast with the age of onset of GAD cited in DSM5 that has been recorded to be during 30s [3]. Similar data on the earlier onset of GAD has been reported by Angst et al. [27] with an average age of onset 15.6 years, with 75% occurring before age 20. In contrast, the age of onset of major depression associated with anxiety in our sample was later, with 19% during adolescence and 81% in adulthood, with half (41%) having an onset after the age of 30 years. This data is again in contrast with DSM5 [3] that cites the onset of major depressive episode between the ages of 20s to 30s. The onset of panic attacks in our sample was half and half during adolescence and adulthood (49% & 51% respectively), mostly in their 20s (47%).

An admixture analysis to identify the age of onset in GAD, derived from 459 adults with such diagnosis as a part of the Netherlands Study of Depression and Anxiety (NESDA), revealed a bimodal age of onset: an early-onset before age 24 years, and a late-onset past 24 years of age. Multivariate analysis revealed that early-onset GAD was associated with the female gender, higher education, and higher neuroticism, while the late-onset GAD was associated with physical illnesses [28]. Since GAD starts manifesting in childhood (16%) and adolescence (77%) with 93% of cases in our data before adulthood, it would be more realistic to investigate all types of anxiety in this age group, such as separation anxiety, in a time continuum that may evolve into GAD later on in life.

The Prevalence

Of 295 patients with mood disorders seen in our clinic during the three months of May–July 2019, 38.30% (113 sample subjects) were diagnosed with GAD. Therefore almost 4 out of 10 mood disorder patients having GAD calls for a more accurate general population survey to identify the true prevalence of Generalized Anxiety disorder that could be beyond the current estimate of DSM5 [3] at 2.9% prevalence in US and .4–3.6% in other countries. In a recent WHO epidemiology survey of college students world wide [29], the 12-month prevalence of GAD has been 16.7% that if we add the prevalence of panic disorder (4.5%), the GAD prevalence will be 21.2% and more than the prevalence of major depression (18.5%). This still leaves social anxiety disorder and any other anxieties that could be easily recognized within a general term of GAD.

An Ontario epidemiological study of mental disorders in children and adolescence recently by Georgiades et al. [30] has also shown the six-month prevalence of GAD 3.4% in children (4 to 11 years) and 9.70% in teenagers (12 to 17 years). If we add "any anxiety" (a vague disease category in many epidemiologic studies) (8.72% in children & 14.85% in youth), and social anxiety (2.99% in children & 3.43% in youth) to GAD as a common pathway anxiety, the six-month prevalence rate of this disorder jumps to 15.11% in children and 27.98% in adolescence, still without counting in PD. The prevalence of pure GAD alone even in a rural region like Amazon, Brazil has also been reported recently to be as high as 8.4% [31]. In another epidemiologic study in Tanzania, the prevalence of depressive and anxiety symptoms among out-of-school adolescent girls and young women were 36% and 31% respectively [32]. These high rates of anxiety in different parts of the world with differential environmental factors including the level of stress, leads us more to the concept of GAD as a genetic entity or susceptibility to manifest clinically upon precipitation by environmental factors, predominantly stress.

The Genetics of GAD

The genetic risk of GAD has been estimated in 1/3 of the patients by DSM5 [3], while our data indicated a rate of 62% or 2/3 of our sample. There are also reports of significant odds ratio (2.1 to 2.6) for GAD in children of parents with the same disorder after excluding offspring with major depressive disorder (MDD) or adjusting for MDD and non-GAD anxiety disorder diagnoses [33]. Moreover meta-analytical integrations of family and twin studies have calculated a recurrence odds ratio (OR) of 6.1 and a genetic heritability of 31.6% in anxiety disorders [34]. Also, in comparison with depression, a common factor has been accounted for most of the genetic influence on generalized anxiety, separation anxiety, social phobia, and panic [35].

It has also been proposed that a common underlying genetic additive factor links GAD to a cluster of internalizing conditions, e.g. social anxiety disorder, PD, agoraphobia, posttraumatic stress disorder, burnout, and MDD in several genetic and twin studies [36–39]. Twin studies have also reported high genetic correlations between GAD and several dimensional traits related to GAD, e.g. neuroticism, with an overall correlation of 0.80 [40–43]. In regard with genetic stability of GAD, a 40-year follow up studies of a sample of patients suffering from GAD in Spain, the prevalence of this disorder was reduced only from 20% to 17% with not much improvement over time [44].

Conclusion

Generalized Anxiety Disorder (GAD) due to its high prevalence, early age of onset extending across the life span, its generalization in different contexts, complications and extensions to other anxiety and mood disorders, is in an urgent need of re-visitation. The reconsideration of GAD as a common anxiety disorder pathway or an underlying anxiety entity that we propose here, will make this condition as the most common mood disorder or perhaps of any psychiatric disorder. This will include an evolution of anxiety due to a genetic susceptibility or sensitive temperament, negative affectivity or neuroticism with tendency to internalization [16–18, 33–43] across the life span to a variety of anxiety phenotypes, e.g. separation anxiety, performance and social anxieties, panic disorder and even depression caused by anxieties [19–28]. Hence, social anxiety could be seen as a variety of GAD; panic disorder as an escalation of this anxiety disorder; and major depression mixed with anxiety as an untreated prolonged GAD. Therefore, additional longitudinal studies of childhood and adolescent anxiety disorders and their developmental course evolving into different anxiety and mood disorders in adulthood are imperative.

As the most hereditary mood disorder or even any psychiatric disorder (62% or 2/3 in our data) a comprehensive GAD needs to be recognized as such with earlier diagnosis and treatment. The genetic risk of GAD could manifest at a clinical or observational level as a phenotype of "sensitivity", negative affectivity or "mood over-reactivity" early in life that gives rise to anxiety disorders manifestations upon interactions with the environmental stimuli or stress. Therefore cross sectional categorizations and studies of different anxieties that could be multi-facets of a generalized anxiety with a common pathophysiological pathway is evasive and arbitrary, leading to under-recognition, ineffective treatment and lack of prevention.

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Author's Contributors Dr. Mostafa Showraki (MD, FRCPC) has been the principal and corresponding author.

Tiffany Showraki has collected and calculated the data that has been reviewed and approved by Dr. Showraki, the principal author.

Dr. Kimberly Brown (PhD.Cand) has edited the final version of the paper before submission for publication.

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Kimberly's ongoing academic career includes a B.A. (Hon), at The University of Toronto in Psychoanalytic Thought with a triple minor in Psychology, Sociology, and Gender Studies. An M.A. in Theory and Policy Studies, at the Ontario Institute of Studies in Education at The University of Toronto, with her current upper level candidacy in Ph.D., studies in the Department of Sociology and Equity Studies in Education at The University of Toronto. While at The University of Toronto, Kimberly was Founder and President of The University of Toronto Psychoanalytic Society for seven consecutive years. Kimberly is a graduate of the Toronto Institute of Relational Psychotherapy and is a registered Psychotherapist specializing in traumatic stress.

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