REVIEW ARTICLE

Narrative Review: Genetic Findings in Patients of Generalized Anxiety Disorder

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ABSTRACT

General anxiety disorder is a chronic disorder. The prevalence of GAD is variable in different part of world, with some region having higher figure than others. It's uncertain to quote if the variation is due to genetic loading or environmental factors. It is twice more common in females than males. It has constituted substantial burden on global economy as well as over all quality of life of an individual suffering from GAD. The prognosis of GAD is mainly correlated with the environmental constraints. However, the efficacy of response to pharmacological intervention is better explained on biological model. Certain studies are done to widen the ground of genesis of GAD. Although, by and large it still remains debatable about distinctive gene causing GAD. Nonetheless, the alteration of gene coding of 5-HTTLPR of serotonin is relatively favorable finding in studies, both independently done on GAD and in parallel to other anxiety disorders and psychiatric morbidities.

Keywords: Generalized Anxiety Disorder, genetics, neurobiology

INTRODUCTION

Generalized anxiety disorder (GAD) is a long standing and relapsing psychiatric disorder. It is a composite of unrestrained and often irrational uneasiness. There is apprehensive anticipation about events and activities; associated with 'feeling keyed up,' 'easily fatigued,' 'inability to concentrate,' 'irascibility,' 'muscle strain' and 'sleep irregularity.' Minimum three symptoms are required for more day than not 6 months to be diagnosed clinically as GAD.[1]

The lifetime prevalence of GAD is fluid worldwide. It is 5.1% in USA while its 21% in European adults, which is relatively high.[2,3] The female to male ratio is 2:1.[3] However the data of Pakistan is scant. The point prevalence of GAD for females was 39.4% while 23.3% for males in one hospital based study done in Pakistan.[4] This concurs with the finding of one of the study done in India in primary health care setup, ranging from 21% to 57%.[5]

Anxiety disorders amount to considerable economical burden. The average annual medical cost of GAD is $2132. The figure is even more high in primary care patients without GAD, that is $ 2375 versus $ 1448.[6] Patients with GAD have also incapacitated psychosocial functioning and work productivity. The health related quality of life (HRQL) debility is proportional with patients of depression or panic disorder. GAD with comorbid depression has substantial disability in HRQL than with either disorder alone.[6]

GAD is managed pharmacologically and non-pharmacologically. The medication from different group like selective serotonin reuptake inhibitor (SSRI), tricyclic antidepressants (TCA), serotonin norepinephrine reuptake inhibitors (SNRI), calcium channel modulators, atypical antipsychotics, noradrenergic and specific serotoninergic antidepressant, and benzodiazepines are used. SSRI and SNRI are clinically standard pharmacological regimen for GAD.[7] On contrary, management is insufficient without psychological intervention in most of the cases. Cognitive behavioral therapy (CBT) is considered the gold standard. Nonetheless, other options like applied relaxation, psychodynamic approaches, internet computer based CBT, mindfulness techniques, interpersonal emotional processing therapy metacognitive model and wellbeing therapy have all shown beneficial effects in treating GAD.[8] Despite availability of the effective interventions, only 20-32% are adequately treated

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in primary care. It is mainly due to less up to the mark detection of GAD.[6]

The estimated remission of GAD with passable intervention in five years time is 0.38. The insubstantial remission is in correspondence with low overall life satisfaction, poor spousal or family liaison, unemployment, a parallel personality or substance disorder and a low global assessment score.[9]

GAD is a considered a complex genetic condition. The basis of which involves the effects of multiple genetic and environmental factors that interface throughout the life span to engender the illness. It's been one of GAD's defining facet to have dual diagnosis.[10] This comorbidity complicates phenotypic characteristics for genetic researcher. It raises the argument if it's pertinent to study GAD individually or in association to its comorbid. However, this paper comprises thorough review of genetics of GAD on molecular level, and in relation to other internalizing disorders.

THE NEUROBIOLOGY OF ANXIETY

The neural processing has been studied in humans by exposing the individuals to wide range of threatening stimuli.[11] Such stimulating cues are perceived in the association cortex where they are projected into the thalamus and the amygdala. There is hyperactive response of amygdala and Insula.

The amygdala is a limbic brain structure that has been known as a "neural watchdog' in so far as it responds quickly even before conscious awareness to stimulating cues.[12] The insula is pertinent in interoception; mediating the brain regulation of arousal and aversive states.[13]

Information is then directed from amygdala to frontal cortex and to the paraventricular nucleus for activation of pituitary gland and stress related hormones. The dorsal anterior cingulate and medial prefrontal (ACC/mPFC) monitors the autonomic response, environmental demands, orient to salient events, and properly contextualize negative response. The ventral ACC/mPFC regulates the extinction of excessive emotional reactivity.[14] GAD is uniquely associated with hypoactivity in these regions along with behavioral evidence of impaired emotional conflict regulation.[15]

On the other hand, information is gathered via hypothalamus pituitary adrenal axis (HPA) signals down stream to the pituitary release of adrenocorticotropic hormone (ACTH) to promote the secretion of the glucorticoid hormone, cortisol from adrenal cortex. The increase production of cortisol is the key feature of strained state.[16] Cortisol has well documented anti-inflammatory effects. Nevertheless, paradoxically the stress up regulates the HPA axis and down regulates the sensitivity of receptors for glucocorticoid on immune cells. This limits the efficacy of cortisol to inhibit inflammation.[17]

This overall brain neural circuitry also regulates the autonomous system (ANS), both sympathetic and parasympathetic. The mPFC influence the ANS indirectly through inhibitory effect on the amygdala and directly through projection to both components of ANS. The sympathetic activity trips the locus ceruleus where catecholamines are released through out the neocortex to precipitate generalized cortical arousal.[18] The release of catecholamines indirectly both activate andinhibit the inflammatory effect. This upregulation of sympathetic activity is inversely related to down regulation of parasympathetic effect of ANS. Hence the parasympathetic effect is the core element of inflammation seen in stressed individual.[19]

The amygdala also connects to hippocampus, which is engaged in learning and episodic memory; and is crucial for explicit encoding of sensory cues. It stores information that gives amygdala the ability to respond that has already been notified to the individual. This is known as anticipatory reaction to symbolic situation.[20] It also facilitates to connect two events or circumstances temporally.[21] The hypoactivity and dysregulation of hippocampus is noted in anxiety spectrum.This region is not studied in depth in human in context of anxiety. However, in animals, the ventral hippocampus mediates endogenous anxiety, where as the dorsal hippocampus is involved in memory, both fear and extinction related memory.

GENETIC FINDINGS

Studies done to assess the genetics of GAD are of three types. First types of studies are done of patients who have known GAD. Second types of studies are those which are done on patients with anxiety disorders. Third types of studies included in this review are from related psychiatric morbidities like depression.

GENETIC FINDINGS IN GENERALIZED ANXIETY DISORDER

Genetics is known to play an important role in the pathogenesis of the GAD.[22,23] GAD was more frequent among the first degree relatives.[24] Large population based twin study concluded genetic factors to be more important as compare to environmental factors in the etiopathology of GAD.[25] A population based study done on female twins found that heritability of GAD to be around 30%.[10]

In order to find out which gene or the combination of genes are important in the context of this morbidity a number of studies have been conducted. GAD patients were found to have a higher frequency of allele STin2.12 in comparison to control.[26] STin2.12 is a variable number tandem-repeat (VNTR) polymorphism.[27] It was found in the same study that presence of this allele increases the odds of a person to suffer from GAD. Gene 5-HTT coding for serotonin transporter was assessed among patients with GAD as compare to healthy controls. It was found that risk of suffering from GAD was significantly increased by the presence of 5-HTTLPR–SS functional polymorphic region linked with 5-HTT gene.[28] Another study explored new variants in 5-HTTLPR and concluded that it serves as a promoter region for serotonin transporter gene (SLC6A4).[29] This study suggested that different combinations of long and short alleles of 5-HTTLPR might have some role in causation of GAD. The results were inconclusive because of the small sample size. Analysis of the baseline data from a randomized control trial showed a significant association between single genetic polymorphism of PLXNA2-2016 gene and GAD assessed through HAM -A psychic subscale score.[30] PLXNA2 – 2016 gene encodes for plexin A2.[31] PituitaryAdenylateCyclase – activating peptide (PACAP) and PACAP-type1-recepter have shown an important role in anxiety like behavior.[32]

There are some studies, which have explored the role of genetic difference on the outcomes of GAD after pharmacological interventions. It was found that response to escitalopram was better in patients having La+ allele for SLC6A4 gene as opposed to having La- gene.[33] Efficacy of selective serotonin re-uptake inhibitors (SSRIs) for treating late life GAD was absent when La- haplotype for the serotonin transporter promoter region was present.[33] In a study done to assess the role of PACAP/PAC1 genotype, it was found that Asp54Gly (rs2856966) variant of this genotype resulted in a better response to Venlafaxine XR.[32] Brain-derived neurotrophic factor (BDNF) because of rs6265 single nucleotide polymorphism in its gene was shown to effect response to venlafaxine XR when given in patients of major depressive disorder (MDD).[34] Though depression is the most common co-morbid with GAD but when a similar study was done on patients with GAD, rs6265 polymorphism of the BDNF gene didn't affect the response to venlafaxine XR.[35] In a similar multicenter randomized control trial response to venlafaxine XR was not effected by A118G which is a functional variant of OPRM1 gene.[31] Venlafaxine XR was found to have better treatment outcome in patients having rs7997012 single nucleotide polymorphism of G-allele in HTR2A gene, which is the gene for serotonin receptor 2A.[36] Selective Serotonin Reuptake inhibitors (SSRIs) were shown to effect attention when given in patients with GAD. Transcription variants for different serotonin receptors, which included rs6311 for 5-HTR2A receptor and rs11568817 for 5 – HTR1b receptor, affected attention in patients who were on SSRIs.[37]

GAD can alter the genotype of the blood cells resulting in compromised immunity among these patients.[38] GAD can affect the expression of OPN3 gene among females and EIF4EBP3 gene in both genders.[38] Expression of these genes plays an important role in the immune response and therefore vulnerability to important morbidities.[39]

GENETIC FINDINGS IN STUDIES DONE ON ANXIETY DISORDERS

GAD is a type of anxiety disorders therefore the studies done to explore the role of different genotypes in patients with anxiety disorders have directly or indirectly talked about patients with GAD. The heritability ranges from 25% to 35% of all the anxiety disorders except social phobia.[40] A study done to explore the role of intron 2 polymorphism of 5 – HTTLPR gene it was found that individuals having Stin2.12 allele had higher anxiety scores.[41] A study done on women showed Polymorphism for MAO-A gene was more commonly found in patients with GAD and other anxiety disorders. This study didn't find any association between anxiety disorders and 44 bp ins/del 5 – HTT promoter polymorphism.[41] This study also found that Va1158Met polymorphism of COMT gene could be protective against anxiety.[41] Gamma-aminobutyric acid (GABA) receptors are important for the management of GAD as anxiolytics act on $GABA_A$ receptor.[42] SLC6A1 is a gene that encodes GAT – 1 protein responsible for uptake of GABA from the synaptic cleft. Polymorphisms of SLC6A1 gene in the 5-flanking region played an important role in anxiety disorders with panic symptoms.[42] Single Nucleotide Polymorphisms associated with anxiety disorders included rs2930152, rs2697153 and rs956053.[42]

A study done to explore the role of GAD 1 and GAD 2 genes responsible for synthesis of glutamic acid decarboxylase showed that polymorphism of GAD 1 gene is can make a person vulnerable to anxiety disorders. Study on Participants from family blood pressure program showed that short allele of 5-HTTLPR gene and Pro385Ser played an important role in patients having anxiety trait.[43] By the exploring the role of gene rs4680 coding for catechol-omethyltransferase and Monoamine oxidase showed that this gene don't have any role in anxiety disorder. There was a moderate role of a tandem repeat called MAOA-uVNTR.[44] There was no strong association between single nucleotide polymorphism for catenin-δ2 gene (CTNND2) and anxiety disorders.[45] SLC2A9 gene, which has a strong association with serum uric acid, was explored for its role in patients with anxiety disorders. It was found that this gene might have some

role in social phobia.[46] Findings in epigenetics add make the interpretation of genetic findings related to anxiety disorders even more complicated.[47] Micro RNA (MiRNA) and plays an important role in the stress regulation.[47]

In a study done to explore the effect of anxiety disorder on leukocyte telomere length, it was found that there is no shortening of the telomere length among leukocytes of the patients suffering from anxiety disorder. Alarming finding in the same study was that the patients who had an age between 48 to 87 years had a significant shortening of the leukocyte telomere. This finding therefore supports the argument that patients suffering from anxiety disorders become vulnerable to a number of other morbidities.[48]

GENETIC FINDINGS IN STUDIES DONE ON RELATED PSYCHIATRIC MORBIDITIES

Depression is the most common co-morbidity with GAD. The co-occurrence of GAD with depression is argued because of their common genetic origin. Some experts advocate depression and anxiety as an example of genetic pleiotropy.[27] Therefore genetic association of depression may have some role in the pathology of GAD. It was found that short allele of 5-HTTLPR predicted depression.[49] It is not clear whether this gene directly causes depression or it cause different psychiatric morbidities through stress reactivity.[50] Stress is also an important related condition to GAD. It was found that Cdk5rap1which is a CDk5 regulatory subunit may play some role in the stress.[51]

DISCUSSION

The common characteristic of GAD with other anxiety disorders makes it difficult to establish it as independent entity at biological, genetic, and clinical note. Despite comprehend neural circuitry of anxiety; there are areas that still need more clarification. The ACC/mPFC dysfunction is widely responsible for anxiety like symptoms. However, it is uncertain how this plats onto discrete constellation of symptoms across different disorders of anxiety spectrum. Likewise, the heterogeneity within a single disorder or the way individual compensate for emotional dysfunction over time. On parallel, limited information is known about mechanism of treatment models. The elementary interventions based on animal model may put the barrier toward novel approach.

The heritability of GAD is estimated 30%, which is markedly lower than mood or psychotic disorders. This raisesthe likelihood that major proportion of GAD is explained by individual environmental factors. The argument may be generated on the need to research GAD's genetic make up if GAD is more prone in individuals with unhealthy circumstances. On the contrary, this small figure may be due to limited and mainly inconclusive research done on its genetic.

The gene coding of HTTLPR for serotonin is common basis identified in some of the studies done independently in GAD, and in relation to other anxiety disorders and psychiatric comorbid. Nevertheless, its inter connection to cause variety of psychiatric illness makes it less distinct finding to rely in specifically for GAD. Like its neural circuitry, which is a common pathway in different anxiety disorders; the genesis seems to be also shared since most of the studies composite their outcome on its clinical presentation of common anxiety like symptoms instead of key element of GAD.

The HPA axis takes a significant part to compensate the bodily reaction toward stress as well as metabolic stability. It explains the reason why a strained body is more vulnerable to inflammation. Correspondingly, the shortening of leukocyte telomere length in middle to old age in anxiety disorder is interesting finding since it's likely to have comorbid in this age bracket. However, it needs to be explored more if this shortening of leukocyte telomere exacerbates the features of alreadypresent comorbid in this age bracket or it is a sole reason to have concurrent morbidity.

CONCLUSION

There are many studies done to find out the genetic make-up of the patients suffering from GAD. Nevertheless, these studies remain inconclusive majorly because of small-targeted sample size. Studies that have been done on large sample size have not been replicated in other settings to give conclusive evidence in favor of one or many genes contributing to the causal framework of GAD. It is therefore recommended that adequately powered studies should be conducted in which samples should be collected from diverse populations. The target pool needs to be assessed for different genotypes, which have been reported to play some role in the causation of exacerbation of GAD.

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