

An Update on Genetic and Serotonergic Biomarker Findings in Bulimia Nervosa

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Abstract

Background: Bulimia Nervosa (BN) is a serious Eating Disorder which affects 0.8 - 2.9% percent of the population. The etiology of BN is largely unknown and consequently there is no curative, although psychotherapy and the antidepressant fluoxetine provide symptomatic relief. Biomarkers for BN could support in understanding the pathophysiology of BN, and potentially in diagnosing, and monitoring effects of treatment. This review describes genetic and serotonergic biomarkers for BN.

Methods: A literature search using PUBMED (20 June 2017) was done using the following search terms: 1) "Bulimia Nervosa" AND "biomarker" which gave 58 items; 2) BN AND "gene", "genetic", and 3) BN AND serotonin, which yielded 342 items. Furthermore, articles of interest were retrieved from the reference lists of the identified articles of the first PUBMED search. The main findings on genetic and serotonergic biomarkers summarized.

Results: Heritability, twin and targeted genetic studies support a genetic contribution to the risk of BN. Although there are conflicting findings, 5HTTLPR polymorphism has been found to be linked to BN, especially to the emotional symptoms of the disorder. Several biomarker studies find support for a serotonergic disturbance in BN, and, the Selective Serotonin Reuptake Inhibitor fluoxetine provide symptom relief.

Conclusions: Recent studies support a genetic contribution to the risk of BN and although there are conflicting findings from targeted gene studies on 5HTTLPR polymorphism in BN, several other findings support a serotonergic disturbance in BN.

Keywords: *Bulimia Nervosa; Biomarker; Gene; Serotonin; Pathophysiology*

Abbreviations

AN: Anorexia Nervosa; BN: Bulimia Nervosa; ED: Eating Disorders; 5HT: Serotonin/Serotonergic

Introduction

Bulimia Nervosa (BN) is characterized by repeated episodes of binge eating (i.e. excessive food intake paired with a sense of loss of control), and associated with compensatory behaviors for example self-induced vomiting, laxative use, excessive exercise, and/or food restriction. The prevalence of BN is estimated to between 0.8 to 2.9% and, it is more frequent in women with men being affected in only 5% to 10% of cases [1]. About 50% of patients with BN are free of symptoms after more than 5 years, while about 20% continue to fulfill all the criteria of the disorder [2].

Similar to Anorexia Nervosa (AN), BN also carries an elevated mortality, albeit not as extreme as AN [3-6].

In spite of that the condition of BN has been well-known for many years, and cognitive schemas that describe the psychopathology has been well described, the etiology is still unknown [7-9]. A number of risk factors have been proposed for the development of BN, from genetic to psychosocial risk factors, but these studies have also underscored how limited our knowledge is on the etiology of BN [9,10]. The serotonergic system seems to be involved in the etiology of BN [11], and the Selective Serotonin Reuptake Inhibitor (SSRI) fluoxetine is approved for treatment of BN [12]. Taken together, although BN most likely has a multifactorial etiology that involves complex interactions between genes and environment, the serotonergic system may be a major contributor. Using serotonergic biomarkers to explore the disease mechanisms would greatly improve our understanding of the pathophysiology of the disease.

Ideally, a biomarker should reflect an essential and conceivably unique characteristic of the disease. In general, there are three different types of biomarkers: trait, state, and rate biomarkers. A measure of disease trait is a marker such as a genetic mutation that predicts the likelihood of developing a disease. A measure of disease trait may also indicate susceptibility to disease, for instance cholesterol levels and heart disease risk. A measure of disease state is, in essence, a diagnostic biomarker, and indicate the presence of an active disorder. A rate biomarker is a marker reflecting the pace at which the disease is evolving. Biomarkers are usually characterized according to sensitivity and specificity and other measures that describe how accurately a biomarker detects a specific aspect of the disorder or the diagnosis. This review describes some biomarker findings in BN.

Method

A literature search using PUBMED (20 June 2017) was done using the following search terms:

Search 1: (“bulimia nervosa”[MeSH Terms] OR (“bulimia”[All Fields] AND “nervosa”[All Fields]) OR “bulimia nervosa”[All Fields]) AND (“biomarkers”[MeSH Terms] OR “biomarkers”[All Fields] OR “biomarker”[All Fields]). This yielded 58 items.

Search 2: (“bulimia nervosa”[MeSH Terms] OR (“bulimia”[All Fields] AND “nervosa”[All Fields]) OR “bulimia nervosa”[All Fields]) AND (“genes”[MeSH Terms] OR “genes”[All Fields] OR “gene”[All Fields]). This yielded 177 items.

Search 3: (“bulimia nervosa”[MeSH Terms] OR (“bulimia”[All Fields] AND “nervosa”[All Fields]) OR “bulimia nervosa”[All Fields]) AND (“serotonin”[MeSH Terms] OR “serotonin”[All Fields]). This yielded 342 items.

Furthermore, articles of interest were retrieved from the reference lists of the identified articles of the first PUBMED search. The main findings on genetic and serotonergic biomarkers summarized.

Results

Genetics

Several studies have shown a strong heritability in BN and estimates vary between 0.55 and 0.62 [9,13]. Variance in core BN symptoms (especially vomiting) has also been shown to be due to additive genetic factors [14].

Hypothesis driven genetic research, correlating phenotypes with genes, have proposed the involvement of the serotonin system in mainly due to its involvement in a broad range of relevant biological, physiological and behavioral functions, for example body weight regulation and eating behavior [15-19] (see below). In addition, serotonin may contribute to the psychopathological characteristics of several eating disorders (ED) such as perfectionism, obsessionality and impulsivity [20-22]. Moreover, numerous studies have also implicated hyper serotonergic activity as a trait marker in EDs [17,23-25] which as well may predispose for the development of the disorder.

Studies on the gene 5HTTLPR polymorphism have strengthened the hypothesis of an involvement of the 5HT system in BN. In 5HTTLPR polymorphism, the short (s) allele in the promoter region of the 5-HT transporter gene (5HTTLPR) has been associated with low transcription of the 5-HT transporter protein, and, clinically associated with impulsivity, affective disorder, and BN [25,26]. A recent systematic review including seven studies and 1750 patients of which 64.5% were female, investigated the interaction between 5-HTTLPR and an environmental or psychological factor, with an ED-related outcome variable.

The review revealed that using a multiplicative model, the low function (s) allele of 5-HTTLPR interacted with traumatic life events and experiencing both sexual and physical abuse (but not only one) to predict increased likelihood of an ED and bulimic symptoms, respectively. Using an additive model, there was also an interaction between sexual and physical abuse considered independently and 5-HTTLPR, and no interaction with traumatic life events. No other gene vs environment interactions were significant [27].

Albeit convincing, a recent large genome-wide association study (GWAS) has not been able to support previous findings on 5-HTTLPR in BN [28].

Targeted studies have investigated amongst others the serotonin receptor 1D β gene (HTR1B) and found preliminary evidence suggesting a role in susceptibility to development of BN subtypes [29].

Another study that also implicates the monoaminergic system described an overrepresentation of the Catechol-O-methyltransferase (COMT) Val158 allele and an underrepresentation of the medium-activity haplotype in BN with childhood Attention Deficient Hyperactivity Disorder history, which may suggest a role for COMT variants and related haplotypes in BN and its sub-phenotypes [30].

Variants in the oxytocin receptor (OXTR) gene have been associated with bulimic behavior, and a positive association was found between the G allele of OXTR rs53576 and BN in one study [31]. In the BN group, the G carriers showed a high score on the behavioral inhibition system.

Linkage analysis have implicated 10p14 for BN, as well as other behavioral phenotypes across both AN and BN [32]. Candidate gene association identified e.g. BDNF, delta 1 opioid receptor (OPDR1) and AgRP [33,34]. The advent of GWAS have demonstrated linkage peaks for BN on chromosomes 10p13, and 14q22-23 [35].

Since there seem to be mutual both genetic factors and phenotypic characteristics in AN and BN especially, but also ED Not Otherwise Specified (EDNOS), and there is a considerable rate of cross-over between AN, BN and EDNOS, ranging between 4 and 36% [36-39] it has been proposed to describe them together. In addition, family studies have revealed that AN and BN do not aggregate independently within families, but rather that the risk of developing both disorders is elevated in family members of individuals with an ED [40,41]. Furthermore, a Swedish twin study, approximately half of the genetic factors contributed to liability of both AN and BN [42]. Future studies will need to clarify the relation between the three diagnostic groups further.

Serotonergic Biomarkers

The serotonergic system

A serum tonic factor found to be released from platelets during blood clotting, was discovered, and described as a monoamine named serotonin by Rapport, Green, and Page in 1948 [43]. This amine was found in the highest concentrations in the small intestine and in the brainstem, with lesser concentrations throughout the brain [43]. In the brain, the serotonergic system has an extensive innervation of cortical and subcortical target areas that allows it to influence many brain functions. Furthermore, the serotonergic system has over a dozen serotonin receptor subtypes [43].

Serotonin and behaviors associated with BN

The association between disturbances of the serotonergic (5-hydroxytryptamine; 5HT) system and appetite dysregulation is well established [15,16,18,44-47] and in addition, relevant also in anxious and obsessional behaviors and extremes of impulse control [48,49]. In addition, several studies have found evidence of disturbances of the monoamine function both in acutely ill patients with ED, and after recovery from AN and BN [50].

According to one definition, emotional regulation may be viewed from a multidimensional perspective that emphasizes adaptive responding to emotional distress versus efforts to rigidly control or suppress emotional arousal [51]. Emotional dysregulation is common in BN and plays an important role in the development and maintenance of the disorder [52] and since the 5HT system is one of the major neurochemical systems in the brain involved in emotional processing and regulation [53-56], it can well be assumed that a disturbance in the 5HT system is involved in BN, especially in the emotional dysregulation seen in BN.

Serotonin levels in blood

Several studies have investigated 5HT biomarkers in blood in BN. A study in 15 women with BN and 15 women with recurrent suicidal behavior investigated platelet 5-HT and platelet monoamine oxidase (MAO) activity. Platelet 5-HT was higher in patients with borderline personality than in normal female controls and was positively correlated with the disposition to experience anger. Impulsive personality traits were consistently negatively correlated with platelet MAO activity. Presence of borderline or "multi-impulsive" personality traits/disorder in BN may reflect a greater serotonergic dysfunction in this subset of patients [57].

Another study in 26 BN and 22 HC women investigated impulsive, affective, self-destructive and bulimic symptoms, versus serial blood samples for measurement of [3H]-paroxetine binding in platelets, and prolactin (PRL) responses following oral meta-chlorophenyl-piperazine (m-CPP). The results revealed that bulimic status was associated with markedly reduced density of paroxetine-binding sites, modest blunting of m-CPP stimulated PRL response, and greater nausea following m-CPP. There was no clear covariation between biological variables and most psychopathological or ED symptoms. However, an inverse association (in bulimic women only) between scores

indicating impulsivity and density of platelet 5-HT uptake sites was found. Also in this study was there a link between BN and altered 5-HT functioning, specifically related to impulsivity with reduced 5-HT reuptake [58].

In a study comparing women with full-blown BN (BN; $n = 22$), with BN in remission (BN-R; $n = 11$), and women with no eating or psychiatric disturbances (HC; $n = 22$), platelet [(3) H] paroxetine binding, eating symptoms and psychopathology were measured. The BN-R group showed normal-range scores on eating and psychopathological symptoms, but reductions in density (B(max)) of binding sites for paroxetine similar to those obtained in the actively ill women. Intriguingly, both BN and BN-R had substantially lower B(max) than HC. The results indicate that recovered BN patients have abnormal 5-HT functioning [26], which may serve as a trait biomarker.

In another study 40 female patients with BN was compared to 25 HC with regard to clinical symptoms (eating disturbances, mood lability, impulsivity, and dissociation), childhood sexual and physical abuse, as well as platelet tritiated-paroxetine binding which was done in a subset of the BN patients (27; 11 with Borderline Personality Disorder [BPD] and 16 without; and 16 HC). BN showed greater affective instability, overall impulsivity, and a history of physical abuse than HC. However, the group with BPD and BN showed elevated motor impulsivity, dissociation, and rates of sexual abuse. Paroxetine-binding was found abnormal in BN with no relation to presence or absence of BPD, linking reduced 5-HT transporter density to BN the disorder itself [59].

Yet another study by the same research group, found that in BN, and their mothers, and their sisters, they all displayed significantly lower density (Bmax) of platelet-paroxetine binding than HC, mothers and sisters to the HC. And this finding was also present even when relatives showing apparent eating or psychiatric disturbances were excluded. Moreover, there were significant within-family correlations on Bmax. Taken together, several findings from studies in blood based serotonergic biomarkers indicate a disturbance in this system, and potentially, that there is a heritable trait (or endophenotype), linked to 5-HT activity, carried by BN patients and their first-degree relatives, even when asymptomatic [60].

Another study, which included 20 women with BN and 14 HC and found that BN had significantly reduced number of platelet binding sites and an increase in the affinity for the ligand demonstrated by a lower dissociation constant ($K(d) = 33 \pm 10$ vs. 44 ± 10 pM). Furthermore, a significant correlation between B(max) and K(d) values was found in BN but not in HC [61].

Taken together, there are several studies finding support the notion that BN is associated with a reduction in platelet serotonin transporter density. Furthermore, BN may also be accompanied by an increase in the affinity of the transporter for the paroxetine ligand, as another aspect of a disturbed 5HT function in BN.

Serotonin in the Cerebrospinal fluid in BN

One study has investigated 5HT biomarkers in the cerebrospinal fluid (CSF) and found that recovered patients with AN and BN have higher concentrations of CSF-5-Hydroxy-Indolic-Amino Acid (5-HIAA) compared to healthy controls, levels that are about 50% greater than CSF 5-HIAA levels found in the ill state [21].

Clinical correlates of 5HTTLPR

A study in patients with BN showed that carriers of the s allele of 5HTTLPR showed statistically significant more interpersonal insecurity, affective instability, behavioral impulsivity, comorbid borderline personality disorder (BPD), and a lower density (Bmax) of paroxetine-binding sites. 5HTTLPR polymorphism is proposed as a factor determining proneness to impulsivity, affective dysregulation, and reduced central 5-HT reuptake [26].

Serotonin biomarkers measured in the urine

A study that strengthens the notion of 5HT disturbance in BN, found higher impulsivity, more severe depressive features, and more borderline and self-defeating personality traits in BN than healthy controls. Psychopathological variables were strongly interrelated in BN and they had lower 24-hour excretion in the urine of serotonin and dopamine than healthy controls, as well as lower ability to suppress cortisol [62].

Another study in 75 patients with BN and 30 HC revealed that patients had lower 24-hour excretion of serotonin and dopamine than controls, as well as lower ability to suppress cortisol. The relations between the biochemical and the psychopathological variables were only significant in the BN patients, but not in the control group [62].

Tryptophane depletion studies in BN

Indirect evidence of an involvement of the serotonergic system in BN comes from studies on Tryptophane depletion (TD). TD has been shown to have a mood-lowering effect in subgroups of recovered depressed patients, patients with seasonal affective disorder and vulnerable healthy subjects.

There are a few studies done on patients with BN, and preliminary evidence exists for an effect of TD on BN [63]. In another study, women self-referred for treatment of BN, medication free (n = 26) or who were using SSRI exclusively (n = 13), and HC (n = 25) completed interviews and questionnaires assessing eating and comorbid psychopathology and then participated in a TD challenge. In the TD condition, the groups displayed similar and significant decrements in plasma tryptophan levels and mood [64].

In a double blind, cross/over study tryptophan depletion was done in 10 clinically recovered, medication-free female subjects with a history of BN, and 12 HC. Compared with HC, subjects with a history of BN had significant lowering of mood, increases in ratings of body image concern, and subjective loss of control of eating following the tryptophan-free mixture [65].

Another study in 10 BN and 10 HC found mood lowering, and increased calorie intake in BN compared to HC during tryptophane depletion [66]. Yet another study found similar effects of tryptophan depletion in BN i.e. greater peak depression, mood lability, sadness and desire to binge as compared to HC [21].

Treatment with SSRI in BN

Fluoxetine (Prozac®) is approved in the US for treatment of BN. In the filing for approval, the effectiveness of fluoxetine for the treatment of BN was demonstrated in two 8-week and one 16-week, multicenter, parallel group studies of adult outpatients, that all met the DSM-III-R criteria for BN. The dosing was either 20 or 60 mg/day of fluoxetine, BN patients had moderate to severe bulimia with median binge-eating and vomiting frequencies ranging from 5 to 10 per week. Fluoxetine at 60 mg, but not 20 mg, was statistically significantly superior to placebo in reducing the number of binge-eating and vomiting episodes per week, with the effect present as early as Week 1 and persisted throughout each study. The effect was independent of baseline depression, and the size of the effect was related to baseline frequency, with greater reductions seen in patients with higher baseline frequencies. For the majority, the benefit was a partial reduction in the frequency of binge-eating and purging.

Apart from these registration studies, there have been several studies with fluoxetine and other SSRIs, in BN. One study compared fluoxetine with citalopram, a single-blind study, and found that both treatments showed some effect on outcome measures, but that efficacy profiles were separate. While Citalopram was found useful in depressed patients with BN, fluoxetine may have a more specific effect in patients with introjected anger and BN [67]. Another 12-week study found fluvoxamine more effective than placebo in treating binge eating crises and purging symptoms in BN [68] and yet another study found an effect of all three SSRI, fluoxetine, paroxetine, and citalopram, in treatment of BN over 6 weeks [69].

A biomarker for treatment response may be the short form of the 5-HTTLPR which seem to be significantly associated with a poorer outcome of SSRI therapy in BN [70]. Early studies in depression showed a similar effect [71-73], while recent studies have failed to find a similar association [74,75].

Brain imaging 5HT in BN

Several brain imaging studies have found evidence of a deviation compared to healthy controls in BN in the serotonergic system. One study using positron emission tomography imaging (PET) and the and the radioligands [(11)C]McN5652, which binds to the 5HT transporter, and [(11)C]raclopride, which binds to Dopamine D2/D3 receptors, found no correlations in receptor binding in healthy controls, but that D2 receptor binding was significantly related to harm-avoidance behavior in recovered ED patients, including in BN [76]. A linear regression analysis showed that the interaction between [(11)C] McN5652 binding potential (non-displaceable) and [(11)C]raclopride binding potential (non-displaceable) in the dorsal putamen significantly predicted harm-avoidance, reflecting a direct relationship between 5-HT transporter and striatal dopamine D2/D3 receptor binding in humans, and thereby supporting that 5-HT and DA interactions contribute to HA behaviors in ED [76].

Another study investigated [(18)F]MPPF (4-(2-methoxyphenyl)-1-[2-(N-2-pyridinyl)-p-fluorobenzamido]-ethylpiperazine) binding, which reflects 5-HT1A receptor binding, in the brain of BN patients, and found increased overall binding, as well as increased focal binding in several brain regions e.g. the prefrontal cortex [77]. This increased binding did not covariate with depressive or ED symptoms. In addition, there was a large heterogeneity in binding among BN patients.

In a separate PET study, eight individuals recovered from BN was compared to eight healthy controls with regard to [11C]DASB binding in the brain to assess 5-HT transporter binding. BN patients, albeit recovered had significantly lower [11C] DASB BP(ND) in midbrain, superior and inferior cingulate and significantly higher [11C]DASB BP(Non-Displaceable; ND) in anterior cingulate and superior temporal gyrus in the voxel-based analysis. Region-of-Interest analysis in BN indicated lower [11C]DASB BP(ND) in midbrain, which includes the dorsal raphe, a 5HT nucleus. Taken together, this and previous brain imaging studies indicate that BN have a disturbance in the 5-HT system, also when BN patients have recovered, indicating a pathophysiological trait of the disorder [78].

Conclusion

Several studies find evidence of a genetic involvement in BN. Heritability is increased, targeted gene studies, and association studies support this interaction from genes to behavior in BN. There are also serotonergic genes proposed to be involved in BN, especially the 5HTTLPR serotonergic transporter gene, although there are conflicting findings. Several biomarker studies support a serotonergic involvement in the pathophysiology of BN. Fluoxetine is approved in the US for the treatment of BN and provides symptom relief on BN specific symptoms. The conclusion based upon current knowledge support that disturbance in the serotonergic system is involved in the pathophysiology of BN. From a biomarker point of view, there are no validated biomarkers for clinical use. Most studies have been small, and several suffer from designed issues e.g. low statistical power. Current serotonergic biomarkers remain useful to better understand the pathophysiology of EDs.

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Conflict of Interest

None.

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