

Gender Differences in Autism Spectrum Disorder

By

Sumaya Hossain

18146061

A thesis submitted to the Department of Pharmacy in partial fulfillment of the requirements for
the degree of Bachelor of Pharmacy (Hons.)

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

Student's Full Name & Signature:

Sumaya Hossain

Sumaya Hossain

18146061

Approval

The thesis/project titled “Gender Differences in Autism Spectrum Disorder” submitted by Sumaya Hossain (18146061) of Spring 2018 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on **[date of defence]**.

Examining Committee:

Supervisor:

(Member)



Dr. Sharmind Neelotpol
Associate Professor, School of Pharmacy
Brac University.

Co-Chair:

(Member)

Dr. Hasina Yasmin
Professor & Co-Chair, School of Pharmacy
Brac University.

Dean:

(Chair)

Dr. Eva Rahman Kabir
Professor and Dean, School of Pharmacy
Brac University.

Ethics Statement

This study does not involve any kind of animal trial or human trial.

Abstract

Autism Spectrum Disorder (ASD) is a condition which is related to the development of brain. Gender difference and autism is related to each other as according to many studies it has been found that autism is more prevalent in males compared to females. As females need more severe symptoms to be diagnosed with autism the diagnosis of autism is different between male and female. Not only diagnosis the severity of the symptoms between males and females with autism are different. In addition, there are many evidence that the brain structure of male and female with autism is slightly different. Genetic difference is also found between male and female with autism. Furthermore, the pharmacological effect is also different between males and females with autism. Therefore, this study aims to highlight how gender difference affect different body condition associated with ASD.

Keywords: Autism Spectrum Disorder, Gender Difference, Diagnosis, Symptoms, Neuroanatomy, Genetics, Pharmacology.

Dedication

Dedicated to my parents

Acknowledgement

First of all, I would like to express my gratitude to almighty Allah for making me able to choose this field and study Pharmacy. Without His blessings, I would not be able to complete this project paper and submit it for passing my Bachelor's degree in Pharmacy.

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List of Acronyms

ASD	Autism Spectrum Disorder
SRS	Social Responsive Scale
RB Q	Repetitive Behaviour Questionnaire
CCQ	Children Communication Questionnaire
SSC	Simon Simplex Collection
EDI	Emotional Dysregulation Inventory
CAST	Childhood Autism Spectrum Test
TEDS	Twin Early Development Study
DAWBA	Development and Well-Being Assessment
RRB	Restricted Repetitive Behaviour
SCQ	Social Communication Questionnaire
SCI	Social, Communication and Interaction

Chapter 1

Introduction

Autism Spectrum Disorder or autism represents complex neurodevelopmental disorders or disabilities (Zhang et al., 2020). This neurodevelopmental disorder has some underlying cognitive features and it usually occurs with other conditions. This disorder has attracted many scientists and clinicians for many years due to the behaviour, strength and challenge the people with autism face (Lord et al., 2018). ASD has direct and indirect effects on various sectors which includes health, education, social care, housing, employment and so on having a high economic burden which extends to adulthood.

The people with autism mainly show the social communication and interaction impairment, behaviour repetition as well as intellectual disability in varying levels. Along with these symptoms there are also some psychiatric or neurological disorders which is common with people having Autism Spectrum Disorder. These psychiatric disorders include hyperactivity and problems in attention, anxiety depression and epilepsy. The early intervention of autism in children can help to ease the problems such as communication difficulties in autism. It includes parent mediated interventions, therapist delivered interventions. Pharmacological therapies can also be used for treating some of the symptoms of autism (Lord et al.,2018).

The underlying cause of autism can be environmental risk factors which may include maternal obesity, gestational diabetes mellitus, use valproate during pregnancy, prolonged labour, use of reproductive technology and so on (Lord et al.,2018).Genetic changes can also lead to autism as more than 100 genes and genomic regions have been confirmed to be associated with autism (Lord et al.,2018).These genetic changes alter the sequence of DNA or chromosome structure and cause change in the functional effects of protein coding regions which increases the risk of autism. In addition the altered neural circuits can also lead to autism. From the MRI studies of infants having a high risk of autism has shown the difference in brain structure (Lord et al., 2018). EEG can also be used to know the mechanism or cause of autism which is more economical and can be easily used than MRI (Lord et al.,2018).

The diagnosis of autism is mainly based on the behaviour of the individual. Although there is existence of heterogeneity between and within individual there are some common features of autism through which the clinicians can easily detect autism (Lord et al., 2018). These common features are difficulty in interacting with people, repetitive and, restricted behaviour. In order to diagnose autism in children the parameters which need to be observed are- history of development obtained from parents, the ability of the child to interact with other people. To diagnose autism in adults the childhood developmental data is needed as well as assess the other co-occurring mental disorders (Lord et al., 2018). In addition early diagnosis of autism needs to be emphasized as many studies have proved that autism spectrum disorder can be ameliorated by targeting intensive autism specific service early (Valicenti-Mcdermott et al., 2012).

Early intervention is needed for the management of autism. The result of the early intervention can help the individual to improve their ability for learning as well as parental understanding (Lord et al., 2018). During adulthood the management of autism is mainly based on symptoms associated with autism rather than core symptoms of autism. In addition medications can also be used in autism spectrum disorder. However these medications mainly help to treat the associated symptoms or co-occurring disorders but do not treat the autism directly. The irritability, agitation, self injury associated with autism can be treated with risperidone or aripiprazole although these medications have some side effects which include movement problem, weight gain (Lord et al., 2018).

Gender difference has grabbed the attention of many researchers due to finding differences in symptoms and developmental functioning in male and female with autism. These findings have led to the conclusion that mainly male dominate in autism spectrum disorder and the diagnosis can not be done similarly in male and female as females are diagnosed in delay. The diagnosis of autism in female is a bit difficult while comparing to males as the females need more severe symptoms to be diagnosed as ASD (Masi et al., 2017). In addition the research on autism is mainly on the basis of male phenotype and the diagnosis instrument and procedures are not much sensitive to female and can not diagnose female with autism properly which leads to male predominance in autism spectrum disorder. Thus, understanding the gender difference play a major role showing

symptoms, diagnosis and treatment of autism (Matheis et al., 2019). The following paragraph will show the effect of gender difference on autism and why this study is important.

Many gender studies associated with autism spectrum disorder have shown the evidence of the prevalence of differences of symptoms in autism spectrum disorder (May et al., 2014). For instance, according to some findings, females with autism have shown fewer social difficulties and social functioning compared to males. However, according to some findings there are no differences in these symptoms (May et al., 2014). In addition males mainly show externalising disorders such as Attention Deficit Hyperactivity Disorder as well as oppositional defiant disorder than female (Lai et al.,2019).

However, oppositional behaviours are mainly seen at similar rates in low functioning males and females in autism. In addition females are more likely to show reduced repetitive, stereotyped behaviour and increased self -injurious, compulsive behaviour compared to males (Lai et al.,2019). Autistic females have more linguistic abilities than males and these females have the ability to express social motivation and interest in friendship than males with autism .There is also a term called camouflaging which is mainly seen in females with autism compared to males. Through camouflaging the individual can mask their autistic behavioural appearance. The difference of camouflaging between male and female still needs to be further investigated (Lai et al., 2017). Again these findings lead to a hypothesis that there is a probability that females who are diagnosed with autism or show mild characteristics of autism may face increased adaptation challenges or social difficulties when they enter childhood or adolescent period compared to males (Lai et al., 2017).

Gender differences have the possibility to affect the developmental change associated with autism. For instance, autism diagnosed at the age of 2-4 years and followed up at 6 years old showed the boys are more likely to show intense autism symptoms than girls which indicates that girls have the tendency to attenuate autistic symptoms over time in preschool than boys (Lai et al., 2017). According to some findings girls at the age of 7-13 years with autism showed more adaptive functioning than boys with autism (Lai et al., 2017). Some findings have revealed that females are more protected from autism symptoms which is due to protective mechanism which is the reason

of male bias in autism (Lai & Szatmari, 2020). According to neuroimaging studies there is more substantial change in brain in females with autism than males which reveals that females need to undergo more risk factors such as more genetic mutations to show symptoms of compared to males (Lai & Szatmari, 2020). In addition some researchers found that early overall brain structure over growth appears more in boys at preschool than girls (Lai & Szatmari, 2020). However genes can also affect the difference in autism between male and female according to which males have the more tendency to show the symptoms of autism due to naturally male heightened gene expression in male but females show less symptoms due to the increased expression of protective gene (Lai & Szatmari, 2020).

However, there are some findings which suggests there may be no effect of gender difference in autism spectrum disorder. For instance there was not gender difference on autistic symptoms triad in 37 boys and girls at the age of 3-17 while having ASD (Rivet and Matson, 2011). In addition 20 high functioning girls were examined and they did not show any kind gender differences in the symptoms of ASD (Solomon et al., 2011). Thus there are mixed findings of gender differences in ASD (May et al., 2013). Although there is effect of gender on autism most of the research of autism symptomology is mainly based on male phenotypes but these researches do not include female with autism spectrum disorder (Matheis et al., 2018). This lack of research based on gender can lead to problem where female would remain underdiagnosed and they won't get the treatment they need.

Thus, we can say our current understanding of autism is just male biased but the acknowledgement of gender diversity in autism need to be increased as well as in depth understanding of clinical implication of gender diversity in autism is necessary (Lai et al., 2015). Thus different methods or experiments need to be developed to prove the effect of gender difference on autism spectrum disorder. As there is male biasness in autism spectrum disorder and although there are some contrasting data on effect of gender difference on autism there are many evidence that gender difference does have effect on autism spectrum disorder. Thus this study will help to acknowledge the effect of gender difference in autism spectrum disorder.

1.2 Aim

The aim of this study was to evaluate whether gender difference has effect on autism spectrum disorder.

1.3 Objectives

The objectives of this study were to:

- see the prevalent and reason of gender difference in autism spectrum disorder.
- acknowledge the methods or experiments which are used to prove the effect of gender difference in autism spectrum disorder.

Chapter 2

Methodology

In order to evaluate the effect of gender difference on autism spectrum disorder various search engines for instance journal articles and books have been used. The literature resources that have been used are google scholar, science direct, Elsevier, research gate, PubMed, nature, springer which includes various peer reviewed articles. Different articles on survey relevant to this study were also included.

The key words that have been used in order to search for relevant articles are: Autism Spectrum Disorder, Gender Difference, Female, Male, Diagnosis, Symptoms, Behaviour/Behavior, Neuroanatomy, Genetics.

Chapter 3

Findings and Discussion

3.1 Gender Difference on Diagnosis of autism

Diagnosis of autism is needed to attenuate the symptoms related to it. There are many evidence which shows that gender difference has effect on the diagnosis of autism. In order to evaluate the effect of gender difference on the diagnosis of autism an experiment was done where data was gained from Twin Early Development Study (TEDS) in which children were screened for autistic traits by using CAST (Childhood Autism Spectrum Test) and diagnostic criteria was evaluated using DAWBA (Development and Well-Being Assessment) and through this assessment the diagnosis rate of autism in boys was 56% and the diagnosis rate of autism in girls was 38% which reveals that female are less diagnosed compared to male (Dworzynski et al., 2012). The reason for this less diagnosis rate may be females having autism spectrum disorder are missed in the process of diagnosis and females need additional problems to be diagnosed with autism. Another reason is the male biasness during the diagnosis of autism (Dworzynski et al., 2012) as autism is diagnosed four times more in male compared to female (Loomes et al., 2017).

Another study has revealed that through ASD assessment it is proven that the diagnosis of ASD was higher in males than females as 72% of the males were diagnosed with ASD while 66% of females were diagnosed with ASD which can be due to health practitioners or psychiatrists have less knowledge about how autism symptoms manifest in female or it can be due to the under-diagnosis of female with ASD (Wilson et al., 2016). Again through diagnostic assessment which was done through ADOS (Autism Diagnostic Observation Schedule) and 3Di (Development, Dimensional and Diagnostic Interview) it was found that 55% of the boys and 25% of the girls were diagnosed with ASD which indicates that boys have 2.18 times more possibility to be diagnosed with ASD and the reason of less diagnosis of females according to the researchers was that the RRB (Restricted Repetitive Behaviour) symptoms were less predictive in girls with autism than boys (Duvekot et al., 2017). Additionally according to RBS-R study which is mainly a report of RRBI report revealed the lower score on stereotyped, self injurious and restricted behaviour in female indicating a lack of diagnostic accuracy in female with autism (McFayden et al., 2020).

Social Communication Questionnaire (SCQ) which is a screening method for the identification of autism (Volkmar et al., 2013) has compared the domain of SCQ which is SCI score. According to the findings the SCI (Social,Communication and Interaction) scores were higher in girls which indicates that girls need more severe difficulties to be diagnosed with autism (Evans et al., 2019).

Evaluation of the age of diagnosis of autism in male and female has revealed that the age of diagnosis of autism was higher in female which can be due to females have the less possibility to correctly diagnosed and have the most possibility to be misdiagnosed during the first evaluation of autism than males and another reason for this difference was male phenotype is more obvious compared to female as according to some studies social communication deficits were more observed in male than females with autism. In addition females with autism have the tendency to show interest, communication features which are more acceptable in society thus it is difficult to diagnose female autism (Gesi et al., 2021).

3.2 Gender Difference on Symptoms of Autism

3.2.1 Behaviour

Evaluation of behavioural presentation associated with autism has proven that gender difference has impact on the behaviour of autism (Lai et al.,2020). According to a study the researchers conducted an assessment in order to know the behavioural symptoms associated with autism where the data was mainly gained from parent reported SRS (Social Responsive Scale),CCC -2 (Children's Communication Checklist -Second Edition) and RBQ -II Repetitive Behaviours Questionnaire) (May et al.,2012).

Variable	Boys with ASD Mean (SD)	Girls with ASD Mean (SD)
<u>Social Responsive Scale</u>		
1.Social Awareness	1. 15.56(11.26)	1. 12.78 (3.36)
2.Social Cognition	2. 20.81(13.83)	2. 19.75 (5.41)
3.Social Communication	3. 33.06(15.35)	3. 33.53 (8.76)
4.Autism Mannerisms	4. 20.44(14.89)	4. 19.81 (6.26)
<u>Repetitive Behaviour Questionnaire</u>		
1.Repetitive Behaviour Movements	1. 1.54(0.54)	1. 1.84 (0.60)
2.Rigidity	2. 1.99 (0.60)	2. 2.00 (0.59)
3.Autistic Preoccupations	3. 1.78 (0.46)	3. 1.96 (0.47)
4.Sensory Sensitivities	4.1.63 (0.59)	4. 1.73 (0.53)
<u>Children Communication Questionnaire</u>		
1.Speech	1. 5.94 (3.65)	1. 6.56 (3.91)
2.Syntax	2. 5.91 (3.24)	2. 5.78 (3.87)
3.Inappropriate initiations	3. 5.50 (2.46)	3. 3.94 (1.87)
4.Nonverbal Communication	4. 2.56 (2.43)	4. 2.44 (2.46)

Table 1: Difference in SRS, RBQ and CCQ between boys and girls with autism (May et al., 2012)

Through this assessment it has been found that in boys and girls with autism there is not much difference in social responsive scale however females have shown better social ability. In addition male with ASD has more difficulties with repetitive motor movements which makes the boys with ASD more behaviourally noticeable than girls. Although the difference in other repetitive scale was less between male and female with autism but repetitive behaviours were more impaired in boys (May et al., 2012). This study has also revealed that males have higher levels of hyperactivity than females with ASD. As females with ASD shows less hyperactive -impulsive

behaviour they are clinically underrepresented. This study has also proven that gender difference has also impact related to communication ability with autism (May et al.,2012) as boys with ASD show less appropriate initiation than girls with ASD and boys talk more repetitively than girls to which no one shows any interest. Social and communication deficit was more found in boys with ASD than girls. In addition inappropriate verbal initiation and poorer pragmatic language skill was more in boys than girls with ASD which reveals that the behavioural problems were more obvious in boys than girls (May et al., 2012).

Furthermore, two procedures which are friendship questionnaire (Head et al., 2014) and Friendship Survey (Dean et al.,2014) to know the friendly behaviour associated with autism found no effect of gender difference on friendly behaviour related to autism. However, through friendship quality scale it was found that males with ASD shows lower closeness and helping behaviour to their friends compared to female with autism (Sedgewick et al., 2016).

Another study shows males exhibit more impaired performance according to Trail -Making Test and produce fewer levels of autobiographical memories (Hull et al., 2017). Autobiographical memory Cueing Task has also revealed that males have low autobiographical memory than female with autism (Volkmar et al., 2013).However through recent memory task it was found that there was nor interaction between gender and autism according to which there is no effect of gender difference on memory associated with autism (Volkmar et al., 2013).

Gender difference has also effect on externalising and internalising behaviour associated with autism. At younger age females with autism has more internalising problem compared to male with autism thus females show more depressive and anxiety than males with autism (Hull et al., 2017).This study has also revealed that males with autism show more externalising behaviour problems. However as the children become older the male and female with autism shows similar level of externalising and internalising behaviour proble(Hull et al., 2017).

Additionally, by obtaining data from Simons Simplex Collection (SSC) it has been found that females with autism has more impairment than males. By analysing the cognitive data it has been found that females with ASD have lower cognitive skills as they showed lower overall IQ, verbal

IQ, non verbal IQ compared to males with ASD. However this study has also showed that females with autism have poor adaptive function and more behaviour problem and irritability (Frazier et al., 2014). A table is given below to show the impairment observed in females associated with autism. Although females with autism have shown impairment the male to female ratio is 9:1 which is due to females need more deleterious hit to express autism phenotype or there is etiologically protected factor in females thus they need higher genetic liability to express autism (Frazier et al., 2014).

Characteristics	Females with Autism
1.Restricted Interest	Symptoms are less
2.Irritability	Show more problems
3.Cognitive Skills	Have lower ability
4.Adaptive skill	Less skill

Table 2: Impairment of females with autism (Frazier et al., 2014).

3.2.2 Camouflaging

Camouflaging is a behavioural adaptation in autism spectrum disorder where the individuals with autism mask their symptoms during social situation (Corbett et al., 2021). According to a study in order to know the effect of gender difference on camouflaging related to autism observational and discrepancy method was used where IQ of individual with autism was measured according to Wechsler Abbreviated scale of Intelligence and social reciprocity was measured by Interactive Drawing Test (Wood-Downie et al.,2021).According to this experiment the IQ and social reciprocity was more in female with autism compared to male with autism which indicates that females with autism shows more camouflaging (Wood -Doenie et al., 2020). Furthermore through Camouflaging with Autistic Traits Questionnaire it was found that autistic females have higher camouflaging score than males with autism (Hull et al., 2020). The reason of females

showing more camouflaging may be due to social expectations .Females face more social pressure to hide their autistic traits and satisfy the social expectations due to their gender role (Hull et al., 2019).Moreover females with autism has reported the feelings of loneliness and isolation which is the result of bullying they face (Cook et al., 2018).Thus they develop this behavioural adaptation (Camouflaging) in order to fit into social environment (Schuck et al., 2019). Thus females have more tendency to camouflage their symptoms (Tubío-Fungueiriño et al., 2021).

3.2.3 Emotional Dysregulation

Attenuation of positive emotion and difficulties in the regulation of emotions are often observed in the individuals with Autism Spectrum Disorder which lead to increased risk of affective disorders and problematic behaviour (Zaharia et al.,2021). Gender difference play a major role in emotional dysregulation associated with autism. According to a study through Emotional Dysregulation Inventory which is a caregiver report questionnaire to evaluate the problems associated with emotional regulation it has been found that the female with autism has higher clinically elevated EDI-Rscore than male which indicates that females with autism have more emotional dysregulation than males with autism (Wieckowski et al., 2020) which suggests that females have greater impairment in terms of high emotional intensity and this poor emotionalregulation can happen due to age and cognitive ability as the aged females show more emotional dysregulation (Wieckowski et al.,2020).

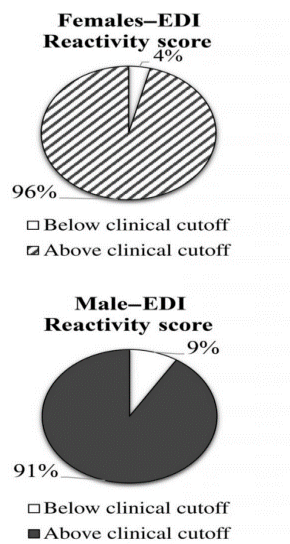


Fig 1:EDI scores of male and female with autism (Wieckowski et al., 2020).

3.2.4 Narrative Skill

Individual with autism has limited narrative competence which affects their everyday life and gender difference play a major role related to narrative competence associated with autism. According to a study through the assessment of narrative competence it was found that 3 out of 11 girls and 2 out of 11 boys have the ability to verbalise core aspect of the story. Although the difference was small but it proves that girls have more narrative competence than boys with autism (Kauschke et al., 2016). This study has also revealed that by assessing the internal state language category which are emotion, physiology, evaluation it has been found that females with autism generate more words for internal states and also they explain more reasons and consequences of internal states than males with ASD. According to the researchers this gender related difference occur due to the females phenotype which is different from male phenotype (Kauschke et al., 2016).

3.2.5 Executive function

In order to know the effect of gender difference on executive functioning associated with autism EF-subtest and WCST (Wisconsin Card Sorting Test) task and verbal fluency task was done .Through the evaluation of executive function domain it was found that 43% of the female with autism and 61% of the male with autism scored below the average (Lehnhardt et al., 2016). According to this study females with ASD showed less impairment in visuo motor skills and more verbal fluency skills which indicate females with ASD have positive effect on motor output and non motor output speed dependent executive function (Lehnhardt et al., 2016).

3.3 Effect of Gender Difference on Neuroanatomy of autism

Through many studies it has been concluded that there are neuroanatomical differences between individuals who have Autism Spectrum Disorder and neurotypical controls (Donovan et al.,2016). In addition, it has also be proven that gender difference has effect on the neuroanatomy of autism

3.3.1 Grey Matter and White Matter

In order to know the difference in grey matter volume between males and females with autism Support Vector Machine analytical approach was used to get information from MRI data where 76 participants with ASD were analysed among them 38 participants were male and 38 participants were female (Retico et al., 2016a). This study has proven that females with ASD have many areas with the likelihood of increase in grey matter volume compared to males with ASD. According to this study males have two regions associated with increase in grey matter volume which are the left middle occipital gyrus (BA19) and R superior temporal gyrus (R STG; BA 22). The volume of BA19 is the reason of behaviour problems in male with autism and R STG volume is related to pathogenesis and language impairment in autism. Females with autism showed increased grey matter volume in right anterior cingulate cortex (ACC and right cerebellum which cause social cognitive and emotional impairment associated with autism (Retico et al., 2016b). In addition the internalising problem for instance anxiety and depression is also related to the ACC volume (Retico et al., 2016b).

Another study has evaluated the effect of gender difference on grey matter volume where 30 males with autism and 30 females with autism participated and the method used for the evaluation was Voxel Based Morphometry (VBM) which is a method to observe difference in volume in an unbiased whole brain mass (Lai et al., 2013). By using 2×2 factorial analysis design on grey matter it has been proven that males have greater volume of grey matter on six clusters of bilateral frontal a females have larger volume of grey matter in different parts of brain (Lai et al., 2013). The figure given below shows the grey matter volume in male and female with autism where the blue color mainly shows the brain part where male with autism has larger grey matter volume and the red color shows the females brain parts having larger grey matter volume.

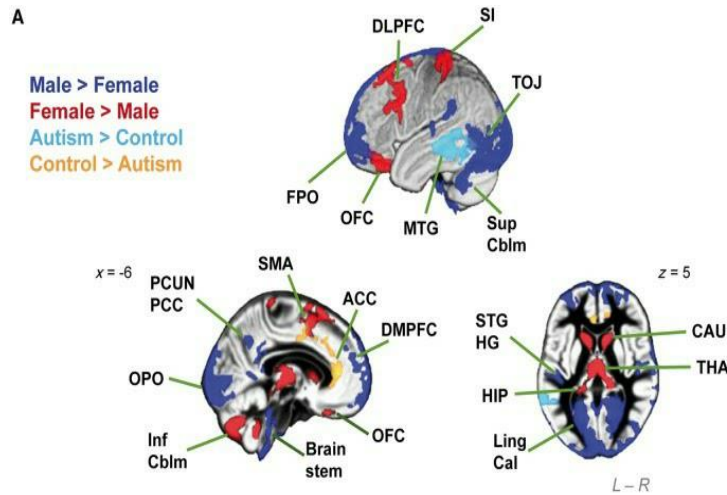


Fig 2 : Grey matter volume in male and female with Autism (Lai et al.,2013)

In this study the difference in volume of white matter in male and female with autism has also been demonstrated. The volume of white matter was larger in six clusters in males with autism and in females the white matter volume was larger in three clusters which proves that autism manifests differently according to gender (Lai et al., 2013). The figure given below shows the grey matter volume in male and female with autism where the blue color mainly shows the brain part where male with autism has larger white matter volume and the red color shows the females brain parts having larger white matter volume.

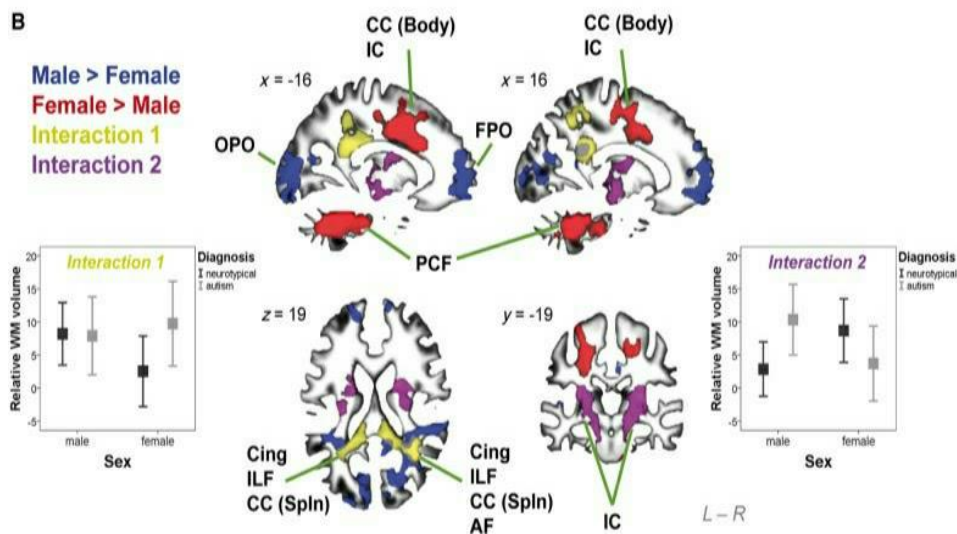


Fig 3: White matter volumes in male and female with Autism (Lai et al.,2013)

Furthermore according to a study by performing MR imaging in order to measure the grey matter and white matter volume in brain and by assessing regional effect by VBM it was found that there is difference in total white matter volume where the white matter is more in males with autism and regional grey matter volume in right parietal operculum and fractional anisotropy as well as corpus callosum and cingulum which reveals that there is significant interaction between gender and autism diagnosis (Beacher et al., 2012).

3.3.2 Functional Connectivity

In order to know the gender related differences in functional connectivity of brain associated with autism the fMRI data from male and females in the Autism Brain Imaging Data Exchange repository was collected. From the data it has been found that males with ASD displayed hypo connectivity and the females with autism showed hyper connectivity (Alaerts et al., 2016). This connectivity cause difference in diagnosis of autism between male and female. However female protective factor protect the females from reaching the threshold for the diagnosis of autism, thus female need more severe etiology to diagnose with autism (Alaerts et al., 2016).

According to another study it has been proven that sensory over responsivity (SOR) is related to functional connectivity in salient network which is a brain network, considered to help to direct attention to the relevant stimuli in a specific environment. Through this study it has been found that gender difference has effect on how SN connectivity is related to SOR symptoms (Cummings et al., 2020) and show difference in symptoms such as social function between male and female ASD. SOR connects quite differently with SN in female with autism compared to male with autism thus the females have higher level of SOR which is the reason that they show more camouflaging. In addition the SN connectivity with SOR in female is also related with sensory seeking and pain perception (Cummings et al., 2020).

3.3.3 Hormones

Higher rate of hormonal dysfunction disorders are associated with autism which indicates that hormone have effect on autism (Ferri et al., 2018). According to sMRI studies it has been proven that sex steroid hormone has effect on brain structure which is related with the interaction of gender and diagnosis of autism (Tan et al., 2020).The brain volume in autism is also related with androgen exposure as ventro medial prefrontal and dorsal anterior cingulate volumes are modulated due to androgenic receptor allele efficiency which causes female to show higher ASD symptoms severity (Bedford et al., 2020) and this effect is not observed in male with ASD. Furthermore due to androgen exposure the white matter volume is increased in males compared to female with autism (W. Zhang et al., 2018). And according to the findings it has been proven that androgen exposure is high during early development of sexes in ASD (Walsh et al., 2021). Additionally the masculinization in females with autism is relayed to elevated level of testosterone hormones (Walsh et al., 2021). Furthermore according to another study it was found that due to neonatal testosterone administration the oxytocin expressing cells were decreased in a greater extent in males with autism where oxytocin hormone helps to bond trust and social communication. In addition oxytocin hormone is considered as treatment in preclinical trial but it works differently in male and female with autism as due to oxytocin administration males show improved worked memory and social gaze compared to females with autism (Walsh et al., 2021).

3.4 Role of Gender Difference in Genetics of Autism

Studies have found many genes are related to Autism Spectrum Disorder for instance the copy number variants (CNV) and single nucleotide variants (SNV) are associated with ASD (Klei et al., 2012). The effect of gender difference in genetic basis of autism has not well studied but there are many studies which suggest that girls have more possibilities to be genetically protected from autism (Jacquemont et al.,2014). Additionally females with autism exhibit more detrimental CNVs and SNVs than males with autism. Thus it is concluded that gender difference have effect on genes associated with autism (Jacquemont et al., 2014).

Females show protective effect due to the regulation of many genes. Furthermore the autistic girls show lower cognition which is due the extra genetic mutation in autistic girls (Jacquemont et al., 2014). In order to females be diagnosed with autism they need more disruption in gene compared to male with autism (Robinson et al., 2013). The CNVs in autistic female disturb the functional network of gene which is involved in synaptogenesis, neuronal motility to a greater extent than male with autism (Gilman et al., 2011).

According to a study the linkage signal which is seen at 1 p31.3, 5q12.3, and 9q33.3, 133.16cM on 7q chromosome, 11 q13.4, 17 q11,17q21 and microdeletion which is seen at SHANK1 are observed in males with autism (Chen & Van Horn, 2017). In addition males with autism show DRD1 polymorphism which encodes dopamine D1 receptor (Chen & Van Horn, 2017). Mutation is also seen at rs -265981-C,rs-45321-A,rs-686-T haplotype and this genotype causes difficulties in non verbal communication, social interaction in males with autism. Additionally by the use of GWASA it has been proven that 5 SNPs on 13q33.3 chromosome and paternal transmission of SNPs rs2535443,rs31115 on XG gene on Xp22.33 chromosome is related to males with autism (Chen et al.,2016).Another case control study has proven that NLGN3 gene and variants at SNP rs484425 as well as haplotype XA-XG-XT are observed in males with autism (Yu et al., 2011).

Females with autism shows deletion at chromosome Xp22.3 as well as linkage signal at chromosome 4,8p12 and 8p21.2, 5p15.33,9p24.1 and 11 p 12-13 and 15 q (Chen & Van Horn, 2017). Furthermore according to a case-control association study it has been proven that autistic females have higher prevalence of SNP rs6152 -A and short CAG alleles and according to a family based analysis it has been found that 23 repeat GGN allele is overly transmitted to autistic females (Chen et al.,2016). In addition according to GWAS analysis it has been found that there are 133 common variants which are close to genes related to autism which explains that 5% genetic variance is seen in females with autism whereas 1% in male with autism (Carayol et al., 2014). The figure shown below the loci related with autism where the red color shows the loci which is related to the male with autism and the yellow color shows the loci related to males with autism.

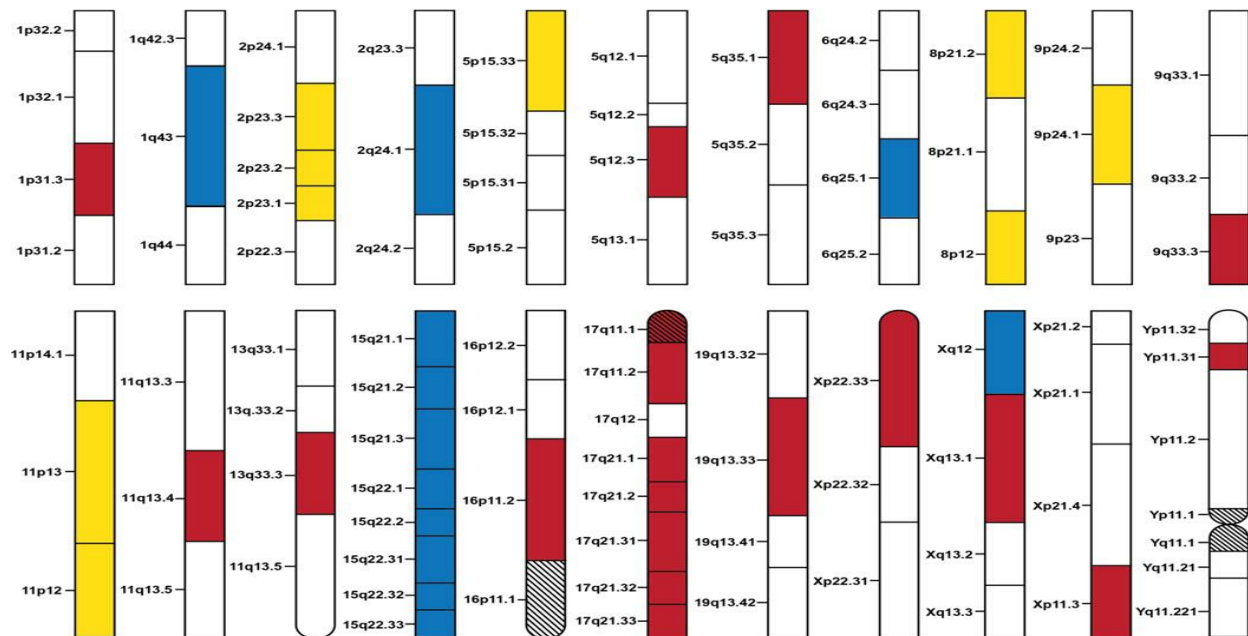


Fig 4: Loci related to autism (Chen et al., 2016)

Furthermore, according to another study through the De Novo Mutation analysis it has been found that females with autism show more DNMs such as de novo loss of function and missense mutation than males with autism (Zhang et al., 2020) which provides enough evidence to support the 'female protective model' for which females need higher minimum threshold to reach autism phenotype. In this study 174 genes were prioritized which were characterized in 3 classes among them there were female specific gene, male-specific gene and shared gene which can reflect the gender bias in autism. However through this study it has also been proven that these three subclasses of genes are co-expressed in brain samples of females which cause autism candidate genes to be filled up by this coexpressed gene in females compared to males thus males show high prevalence as well as this data brings accurate evidence in support of female protective effect (Zhang et al., 2020).

3.5 Effect of Gender Difference in Pharmacology Associated with Autism Spectrum Disorder

Treatment without drug has been proven to be effective for the core symptoms of autism. However some psychiatric disorders which is considered as co-morbidities need to be treated through pharmacological action (Green et al.,2019).The symptoms which can be treated through medicines are: self-injurious behaviour, hyperactivity, impulsivity, mood swings, depression, anxiety as well as sleep disturbance (Green et al.,2019).

According to a study until now no effect of sex difference in response to drug treatment in autism has found. Thus more clinical trial is need to know the effect of gender difference in pharmacological action of autism spectrum disorder. According to the study gender difference for pharmacological intervention in ASD need sufficient statistical power as well as enough number of subject of ASD is needed. In addition female subjects with ASD need to be more in order to know the effect of gender difference (Green et al., 2019).

However while giving psychiatric medications to females with autism some special considerations should be given (Green et al., 2019). For instance the researcher talked about aripiprazole which is an antipsychotic drug being approved by FDA in order to treat the irritability associated with autism in children and adolescents (Green et al., 2019). As aripiprazole is a partial agonist in dopamine receptor it may increase the level of prolactin which may cause gynecomastia and galactorrhea and it can cause side effect in males with ASD (Green et al., 2019). Valproic acid is often recommended for the treatment of mood swings or bipolar disorder associated with autism. However it can cause polycystic ovary syndrome in females of child bearing age with autism which can cause infertility, obesity, heart disease, diabetes (Green et al., 2019). Furthermore some medications for instance modafinil, carbamazepine, lamotrigine which is used to treat psychiatric conditions associated with autism can reduce the effect of birth control pill and can make the individual to become pregnant unexpectedly (Green et al., 2019).

Chapter 4

Conclusion

Finally, it can be said that there are many evidence regarding the effect of gender difference in autism spectrum disorder in different factors for instance in diagnostic sector, symptoms, neuroanatomy, genetical sector and so on. In addition as this gender difference have serious effect in autism spectrum disorder further study is needed in this sectors and the reason behind the further study is given below.

However, though gender difference has effect on autism spectrum disorder there are not enough researches regarding this topic as many research is based on the phenotype of male of autism spectrum disorder (Matheis et al.,2018).In addition the tests to know the effect of gender difference in autism spectrum disorder were not done in population based (Disord et al.,2015) as most of the tests were done in referred sample (Duvekot et al.,2018) and in some experiments the sample sizes are mall which can be an obstacle to get enough information.Difficulties are faced by the researcher as as autistic people have more tendency to be gender non-conforming compared to non-utistic people. Additionally in many experiments male samples were large than the female sample and it has been observed in both autistic and non-autistic people (Sedgewick et al.,2019). Moreover many studies did not consider about the age during the analysis of the effect of gender difference in autism spectrum disorder which is an important factor (Retico et al.,2016).

Furthermore how neuroanatomy and genetics is associated with gender difference is not enough studied (Chen et al., 2016) and due to extreme male brain theory the neurological phenotype reflects hyper masculinization (Walsh et al.,2021). In addition until now data addressing gender difference in response to pharmacological treatment for behavioural problems and other psychiatric condition is not well found (Green et al.,2019).In addition there are many areas which is still not considered while assessing the gender difference in autism spectrum disorder. For instance according to a study while assessing the restricted repeated behaviour (RRBI) there are many unexplored

To conclude it can be said that gender difference has effect in autism spectrum disorder. Thus it is an important phenomenon to examine as it can help to understand the biology of ASD as well as it helps to diagnosis ASD without being bias towards male with autism. In addition it also helps to work toward better treatment strategy (Krishnan, 2018).

4.2 Limitations of the study

Some limitations of this study are given below:

1. Some important resources on ASD, which were used in this study are not recent.
2. Information regarding the effect of gender difference in autism spectrum disorder was not available in context of Bangladesh.

4.3 Future Research Plan

More research is necessary while including increased number of sample specifically females while considering the age of the people. In addition more genetic studies as well as pharmacological studies related to the effect of gender difference in autism can be an important factor for future studies.

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