Co-morbidity in Autism: A Review

A project submitted
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Dedicated to my parents

Certification Statement

This is to certify that the project titled "**Co-morbidity in Autism: A Review**" submitted for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy from the Department of Pharmacy, HONS, BRAC University constitutes my own work under the supervision of **Dr. Sharmind Neelotpol**, Associate Professor, Department of Pharmacy, BRAC University. All of the work described here is entirely my own, unless specified otherwise and that appropriate credit is given where I have used the language, ideas or writings of another.

Signed,

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Countersigned by the Supervisor

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Abstract

Autism spectrum disorder (ASD) is the most prevalent form of neurodevelopmental disorder that interferes with social communication and behavioral development. Most of the toddlers with ASD also show other psychiatric and/ or medical issues. This disorder is known as ‘comorbidity’, and the conditions associated with comorbidity are defined as ‘comorbid’ conditions. The most common comorbid conditions seen in autism are tourette syndrome, tuberous sclerosis, ADHD, sleep problem, epilepsy and seizure, gastrointestinal dysfunction, fragile X syndrome etc. Other conditions, such as, obesity, intellectual disability, OCD, fragile X syndrome, depression, bipolar disorder, motor difficulties, down syndrome may also involve. This poses some serious challenges. For instance, as several conditions are associated, differentiating among the symptoms becomes a serious issue. It also interferes in selecting medication and treatment in according to their root cause so that the choice of treatment does not deteriorate other conditions. Therefore, the aim of this study is to highlight the co-morbid conditions associated with ASD, their symptoms, probable causes, present treatment/ management available by reviewing different reputed articles.

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Lists of Acronyms

ASD: Autism Spectrum Disorder

DSM: Diagnostic and Statistical Manual of Mental Disorders

CDC: US Centers for Disease Control and Prevention

OCD: Obsessive Compulsive Disorder

ADHD: Attention Deficit Hyperactivity Syndrome

DAWBA: Development and Well-Being Assessment

CARS: Childhood Autism Rating Scale

3di: Developmental, Diagnostic and Dimensional interview

DISCO: Diagnostic Interview for Social and Communication Disorders

TS: Tourette syndrome

TSC: Tuberous Sclerosis Complex

FXS: Fragile X Syndrome

ID: Intellectual Disabilities

PDDs: Pervasive Developmental Disorders

ADI-R: Autism Diagnostic Interview- Revised

AEDs: Anti- Epileptic Drugs

AAP: American Academy of Pediatrics

CNV: Copy Number Variants

Chapter 1: Introduction

Child specialist, Leo Kanner reported some unusual behavioral disorder among eight male children and three female children in 1943. They were comfortable and happy when alone. They never cried to travel with mother, but did not notice the time of their father's return from outside and they were not exultant visiting relatives. They were also confused about when and how to smile or how to make stereotyped movement of hands and fingers. They had a literal, inflexible meaning of words. In 1944, a pediatrician, Hans Asperger, also described some other different kinds of behavior in a 6 years old boy named Fritz who 'behaved like adults, learnt to speak at a very early period, never were happy playing with children, and felt shy talking to strangers' (Kanner, 1943).

These reports portray vividly the characteristic behavioral disorder what we now know as Autism or Autism Spectrum Disorder (ASD). The term spectrum reflects the wide variation in difficulties and challenges faced by the patient and their families. These conditions, in most cases, result from some etiological factors such as mutation of gene. However, they may also develop from a set of different neurodevelopmental conditions. In most cases, the previous reports showed that it was the result of the complex "genetic and non- genetic/ environmental factors" interaction. These types of specific behaviors direct to the atypical social development and communication and so these unusual restrictive and repetitive behaviors collectively refer to as autism or autism spectrum disorder.

The Diagnostic and Statistical Manual of Mental Disorders (DSM-III) - third edition, developed the very first operational definition of autism that was published by the American Psychiatric Association. It states that the impairment of the social development appeared before or within 30 months of child's birth. This statement followed by the subsequent revision of the fourth edition of DSM-IV was modified where autism was considered as pervasive developmental disorder, asserted by the earlier "triad of feature" onset, which are impaired communication, restrictive and/or repetitive behavior and stereotyped activities.

In May 2013, the latest revision of DSM-V adopted the umbrella term ASD or autism spectrum disorder by reorganizing the triad by a dyad of features which are-

- Difficulties in social interaction and communication
- Repetitive and restricted interest, activities or behavior

This helps in-

- Providing an improved description of the key features of autism and
- Allowing the proper assessment of clinical services or individuals' "need for support" (Lai, Lombardo & Cohen, 2013).

Comorbidity is a term used when two or more disorders occur in the same person at the same time (Matson & Nebel-Schwalm, 2007). Chronic and debilitating symptoms associated with ASD can co-occur with other conditions or difficulties such as intellectual disabilities, co- morbid psychopatholoies as well as other physical conditions and challenging behavior. However, comorbid conditions associated with ASD is relatively a new notion in the field of research of ASD (Matson & Goldin, 2013). US Centers for Disease Control and Prevention (CDC) conducted an assessment which shows that autistic children had higher chances of medical conditions such as allergies, severe headache/ migraines, seizure, respiratory infection and asthma than general children (Kohane et al., 2012). Many conditions can occur along with autism. For example, anxiety, depression, obsessive compulsive disorder (OCD), obesity, seizure, tourette's syndrome, tuberous sclerosis, gastrointestinal dysfunction, attention deficit hyperactivity disorder (ADHD), sleep problem, epilepsy and seizure etc.

Co-morbid conditions along with ASD are a serious issue. Because the exact cause of these conditions are not yet discovered. Therefore, the treatment for these conditions is also unknown. This concept of comorbidity in ASD is relatively new. For instance, the DSM-IV states that ASD and ADHD co-occur at a very high rate. This theory was established on the basis that they cannot be diagnosed at the same time (Matson & Goldin, 2013). Therefore, this concept is developing a completely new field of study that can be best described by the term 'comorbidity with ASD'.

Aim

The aim of this study is to find out the features (symptoms, causes and treatment) of co-morbid conditions along with autism by reviewing different articles.

Objectives

The research questions addressed in this study are:

- What are the most common forms of comorbid conditions along with autism?
- What are the etiologies and/or genetic mutations associated with these conditions?
- What are the symptoms mostly found when other conditions occur along with autism?
- What are the present treatments available to improve these conditions?

Chapter 2: Method

This review paper has been conducted mostly through different search engines and books. Search engines that had been followed are - google scholar, pubmed, medline, medline plus, mendeley, science direct, researchgate, scopus, which contain peer-reviewed literatures. A wide range of surveys from these research tools was studied to find out information. That information collected from surveys has been used to enrich the review paper. The topics cover all domains from technical to scientific. Different books have been used for basic and additional information. Tables are made based on different tests, surveys and methods from these books and peer- reviewed articles. References have been cross checked to expand the search and also to find out addition information.

Key Words: autism spectrum disorder, tourette syndrome, tuberous sclerosis, ADHD, gene therapy, stem cell.

Chapter 3: Discussion

3.1: Autism Symptoms

Autism comes with interferences in social skill and communication along with other symptoms. An autistic child passes a very tough time interacting with others socially and this problem in social skill is the most prevalent sign of their being autistic. A child being on the spectrum shows social symptoms by the age of 8 to 10 months. These symptoms may include-

- Not being able to respond to their name
- Not having any interest in playing, talking or sharing things or feelings with others
- Particularly being interested in living alone
- Not being comfortable with physical contact
- Not being able to understand emotions of their own and others'
- Hyperactivity (McElhanon, McCracken, Karpen & Sharp, 2014)

Language related symptoms are very prominent in patients with autism. Forty percent of children with autism cannot speak at all. 20 to 30% can develop some skills of sharing through language having special meaning to them and some may lose these skills later. Others include-

- Flat and robotic voice of speaking
- A tendency to repeat the same phrase over and over again- a condition known as Echolalia
- Not being able to differentiate the pronouns like saying "you" in place of "I"
- Having problem with their gesture (Wetherby et al., 2004)

Other symptoms include some of the kinds, which are very serious like-

- Disability in learning
- Obsessive compulsive disorder- OCD
- Attention deficit hyperactivity disorder- ADHD
- Generalized anxiety disorder
- Tourette's syndrome or other tic disorders
- Epilepsy
- Dyspraxia
- Depression

- Bipolar disorder
- Sleep problem
- GI difficulties
- Sensory difficulties (Johnson & Myer, 2007)

3.2: Autism Diagnosis

A large number of instruments are available for the diagnosis of autism spectrum disorders; these can range from formal diagnostic interview to self- completion questionnaires (Matson, Nebel- Schwalm & Matson, 2007). These include-

- Development and Well-Being Assessment (DAWBA)
- Childhood Autism Rating Scale (CARS/CARS-2)
- Developmental, Diagnostic and Dimensional interview (3di)
- Diagnostic Interview for Social and Communication Disorders (DISCO)
- Autism Diagnostic Interview – Revised (ADI-R) (Randall et al., 2018)

Autism spectrum disorder is usually diagnosed on the idea of activity symptoms. There is still a scarcity of relevant etiology for autism. However, substantial analysis has been dedicated for the investigations of etiological factors of autism and related conditions. However, no single cause has been known, genetic, biological and environmental factors are predicted for contributing in autism.

3.3: The Disparities in Global Prevalence and Diagnosis of Autism

The disparities in the prevalence of autism are quite noticeable between developed and developing countries. The key reason behind this is considered to be the diagnostic tools used to measure the prevalence rate. Few studies on autism prevalence have been done in developing countries. Probable causes of this scarcity on research are-

- Stigma problem,
- Shortage of awareness among the people of developing countries on mental health
- Limited number of health infrastructure.

Estimation of prevalence rate is normally the initial step towards the aim of setting in governmental institutions aside with the various nonprofit NGOs' for mental health services. This can also lead to the scientific explanation of cultural- environmental and

genetic basis of autism. A recent pilot study on the prevalence rate of mental disorder, conducted in Brazil, reports that the prevalence of mental disorders, for instance, PDD (pervasive developmental disorder) happens to be 27.2 /10,000 in this region (Paula, Ribeiro, Fombonne & Mercadante, 2011). A prevalence of ASD, in children aged between 0-14, was reported as 1.4/10,000 in Oman, Middle East. Firstly, underreporting and secondly, under-diagnosis attributed to this low prevalence rate in developing countries like in these two cases in Brazil and Oman (Al- Farsi, Al- sharbati, Al- farsi, Al- safaee & Brooks, 2011).

3.4: Risk Factors of Autism

The exact cause of autism is yet to be discovered. There is no single underlying cause that is solely responsible for autism. Therefore, a couple of risk factors is listed for autism to happen. These risk factors are classified as genetic risk factors, neurobiological risk factors and environmental risk factors.

3.4.1: Genetic Risk Factors

ASD is the results of hereditable genetic variations and/or mutations. To find an explanation in support of this genetic link to ASD, different analysis reports have been studied. Some analysis reports show that ASD is additionally common in boys than girls —most probably thanks to genetic variations related to the X chromosome (Chakrabarti & Fombonne, 2005). In a very study conducted by Ozonoff et al. (2011) shows that nearly two hundreds of infants having an older biological sibling with ASD additionally developed this condition. Again, the chance for developing ASD was larger if there was one older affected relative. By the improvement of the availableness of fast, precise gene-sequencing tools and the accessibility of the enormous numbers of DNA samples, important progress in characterizing genetic factors related to ASD has been possible (Coe, Girirajan, & Eichler, 2012; lossifov et al., 2012; Neale et al., 2012; O'Roak et al., 2012; Sanders et al., 2012).

Numerous studies were undertaken to identify the underlying pathogenic mechanisms associated with ASD and so far it has been vividly accepted that ASD has a strong connection with genetic components. This statement has been supported on the basis of the concordance autism rate which has reached up to 90% in monozygotic or identical

twins and only 10% in dizygotic twins (Folstein and Rosen-Sheidley, 200; Veenstra-Vanderweele et al., 2003).

Due to the heterogeneity of this disorder, not any single genetic mutation is solely responsible for more than one or two percent cases associated with autism (Abrahams and Geschwind, 2008). A lot of studies and researches was undertaken which report a large number of genes that has undergone predisposing mutation and/ or polymorphism in different cases of autism. These include- analysis of different linked/ candidate genes, evaluation of chromosomal and genetic variation and GWAS- genome wide association studies. (Abrahams and Geschwind, 2008; Glessner et al., 2009; Ma et al., 2009; Wang et al., 2009; Anney et al., 2010; Pinto et al., 2010; Devlin and Scherer, 2012; Moreno-De-Luca et al., 2013). Aside from that, advancement in the sequencing technique (next generation and exome sequencing) discovered a number of de novo (not found in either parent) mutations, which play an important role as a risk factor of autism (Iossifov et al., 2012; Sanders et al., 2012).

These mutations are classified as rare mutations and copy number variations, which occur in synaptic proteins such for instance Shanks/ProSAPs (Durand et al., 2007), and neuroligins (Jamain et al., 2003). Copy number variation or CNV is a mutation where a specific section of the DNA sequence or genome is either duplicated or deleted followed by affecting a couple number of base pairs. For instance, around 1% of the autism cases are associated with the mutation or deletion of a gene called SHANK3, which produces SHANK3 protein primarily found in the synapse of the synaptic neurons. This protein is important for organizing and co-coordinating other proteins and thus produces a cellular response to the incoming signals. Therefore, SHANK3 involves in motor activity, different emotional behavior and helps in decision-making.

A study was conducted on genetically engineered mice where their SHANK3 gene was made turn off at the time of their embryonic development. Those mice exhibit abnormal motor activity, anxiety, compulsive behavior and they tried to avoid other mice. Later, the gene was reactivated in their adulthood. This results in the elimination of their repetitive behavior and the avoidance tendency. Thus, researchers draw the conclusion that by restoring the functional activity of the SHANK3 gene can help improve several symptoms associated with autism (Durand et al., 2007). Rare mutation can be evaluated

by focusing on the families having a history of severe autism among the female members as ASD seems to be occurred more in male than in female. (Sahin &Sur, 2015)
Moreover, perinatal injury as well as maternal infection such environmental influences play a role in susceptibility to genetic mutation associated with ASD. Cerebellar hemorrhage in premature baby increases the chance of ASD by 30 fold when compared to general babies. Perinatal cerebellar hemorrhage leads to the mutation of COL4A1 gene, which instructs for producing the component collagen type IV and thus play a role in migration of cells, cell proliferation and cell differentiation. Thus, the mutation of this gene can lead to small vassel brain diseases such as porencephaly (Plaisier & Ronco, 2009; Shah et al., 2012).

Other studies have suggested that immune system activation in response to infection during gestation period can contribute to the changes in the brain cytokines in specific region. It can also cause neuropathological changes and thus contribute to ASD. Immune system activation can lead to the mutation of TSC 2 gene that produces tuberous sclerosis complex protein. Mutation of this gene can lead to rare genetic disorders causing the production of benign tumors in the brain and thus causes seizure, delay in the developmental process and intellectual disabilities (Sahin &Sur, 2015).

In addition to this, many other ASD- candidate genes are also involved in other neuropsychiatric disorders. For example, IL1RAPL1 and OPHN1 are involved in X chromosome-linked intellectual disability (Carrie et al., 1999), GRIN1 and GRIN2A-D for schizophrenia (Demontis et al., 2011) and GABRB3 for childhood absence epilepsy (Feucht et al., 1999).

3.4.2: Neurobiological Factors

Genetic code abnormalities also results in abnormal mechanisms during the brain development followed by structural and functional abnormalities of brain, cognitive and neurobiological abnormalities and symptomatic behaviors. Neurobiological differences include-

- Problems with genetic code development involving multiple brain regions, including frontal and anterior temporal lobes, caudate, and cerebellum (Abraham & Geschwind, 2010);
- Structural and functional abnormalities of the brain, including
- Increased gray matter in the frontal and temporal lobes (Carper & Courchesne, 2005; Hazlett, Poe, Gerig, Smith, & Piven, 2006; Palmen et al., 2005),
- Decreased white matter compared with gray matter by adolescence (Volkmar, Lord, Bailey, Schultz, & Klin, 2004),
- Anatomical and functional differences in the cerebellum and in the limbic system (Volkmar et al., 2004);
- Differences in the brain's response to the environment, including
- Decreased neural sensitivity to dynamic gaze shifts in infancy (Elsabbagh et al., 2012);
- Preference for nonsocial versus social processing and hemispheric asymmetries in event-related potentials (ERPs; McCleery, Askchoomoff, Dobkins, & Carver, 2009);
- Disruptions in normative patterns of social neurodevelopment that contribute to a diminished attention to social stimuli (Jones, Carr, & Klin, 2008).

3.4.3: Environmental Factors

Researchers have begun to research on different pre- and post-natal environmental factors (e.g., dietary factors, exposure to medicine and environmental toxicants) which may involve in genetic susceptibleness to cause autism and related disorders. A variety of environmental exposures such as lead, polychlorinated biphenyls (PCBs), pesticides, automotive exhaust, hydrocarbons, and flame-retardants are identified as the major environmental culprits for ASD. (Landrigan, Lambertini, & Birnbaum, 2012; Shelton, Hertz-Picciotto, & Pessah, 2012). Researches centered on the possible environmental risks factors for the event of ASD are somewhat sophisticated, as no specific environmental triggers have been found yet.

3.5: Strategies to Improve Autism

Some strategies are recommended by The American Academy of Pediatrics (AAP) to provide help to a child to improve the overall functions and reach his/her potentials:

- Behavioral training and management: it uses positive reinforcement and self-help to improve social communication skill.
- Applied Behavioral Analysis (ABA),
- Treatment and Education of Autistic and Related Communication Handicapped Children (TEACCH),
- Sensory integration.
- Specialized therapies: Such as, speech, occupational, and physical therapy. For instance, Occupational therapy helps an autistic child to learn how to process information from the different senses like- sight, hearing, sound, smell and touch.
- Medicines: depression, anxiety, OCD and hyperactivity are treated by using different kind of anti- depressants.
- Community support along with parent training: it includes seeking help from a doctor or contact an organization or advocacy group for support and training (Johnson & Myer, 2007).

3.6: Comorbid Conditions Associated with ASD

Many different comorbid conditions can be associated with autism, such as,

- Disability in learning
- Obsessive compulsive disorder- OCD
- Attention deficit hyperactivity disorder- ADHD
- Generalized anxiety disorder
- Tourette's syndrome or other tic disorders
- Epilepsy
- Dyspraxia

- Depression
- Bipolar disorder
- Sleep problem
- GI difficulties
- Sensory difficulties
- Tuberous sclerosis
- Fragile X syndrome

Among those various conditions, a few most common conditions, which co-occur most frequently with autism, will be discussed below:

3.6.1: Tourette syndrome

ASD is often associated with Tourette syndrome (TS). People who have Tourette syndrome show many movement-based and vocal tics. Therefore, it is defined as a part of tic disorder spectrum. This involves both transient and chronic tics. These tics are sudden, involuntary, stereotyped and also repetitive. Tourette syndrome is also known as tourette's disorder, Gilles de la Tourette syndrome and GTS etc. It is also an inherited neurological disorder (Singer & Walkup, 1991). The percentage of autistic children having Tourette syndrome is about 4-5% and about 9-12% has tics of either one kind or both (Kern et al., 2015).

Symptoms

Tic can be considered as simple tics and complex tics. Tics that engage the repetitive movement of few numbers of muscles and which are sudden and brief are known as simple motor tics. Other simple tics may include- blinking of eye, eye movement, and shoulder shrugging or jerking, head jerking and grimacing. Moreover, repetitive throat clearing might be included as simple vocal tics.

On the other hand, tics that engage distinct and coordinated movement of several muscle groups are known as complex tics. Such as, facial grimacing along with head twisting or

shoulder jerking are those of the complex motor tics. Thus, this syndrome is diagnosed in a person when the person exhibits multiple motor as well as one or more vocal tics for more than a period of one year. Therefore, the common tics are summarized in the table 3.1(Ganos & Martino, 2015).

Table 3.1: Common tics in Tourette syndrome

Tics types	Simple tics	Complex tics
Vocal tics	Laughing Grunting Throat clearing Coughing Squeaking Sniffing	Variation in the tone in the same person Swear words Making animal like sounds
Motor tics	Eye blinking Eye darting Nose twitching Head jerks Finger flexing Shoulder shrugging	Facial grimacing Tensing muscle groups Self-harm Touching objectives Flapping

(Ganos & Martino, 2015)

Probable Causes

Although the exact cause of TS is still need to be discovered, current researches show abnormalities in specific region of the brain such as basal ganglia, cortex and frontal lobe as well as the circuits that are interconnecting these regions are responsible for the symptoms of TS. Neurotransmitter (norepinephrine, serotonin and dopamine) are also found to be responsible. Though it is considered as an inherited disorder, the exact mode of its inherency is still needed to be discovered.

Autoimmune processes sometimes contribute to the tics onset particularly-

- The presence of antineuronal autoantibodies
- overexpression of D8/17 B lymphocyte

Therefore, the cause of this syndrome is likely to be as complex as the name suggests (Singer & Walkup, 1991).

Treatment

Treatment primarily focuses on identifying and managing the tics for individual patient. Majority do not require any medication. Only Psychobehavioural therapy, education and reassurance can be helpful. Some relaxation techniques are used to remove the stress that aggravates tics, such as, yoga or exercises. But in extreme cases medications are prescribed to improve the condition and to suppress the tics such as neuroepileptics, antihypertensive agents' stimulants etc. Treatment also depends on the occurring of this syndrome with or without other co- morbid conditions (Singer & Walkup, 1991)

3.6.2: Tuberous Sclerosis

It is popularly known as TSC or Tuberous Sclerosis Complex, which is considered as a rare genetic disease leading to the formation of benign tumors in different parts of the body, and causes other physical conditions like seizure, intellectual disabilities and sometimes delays in development. The tumors are mostly formed in the brain, heart, lung or skin. Though it is present from the birth but does not show immediate problems (Islam & Roach, 2015).

Symptoms

TSC can lead to a lot of health conditions that include epilepsy and seizure, learning disabilities, ASD or behavioural problems, hyperactivity, skin abnormalities such as light colored skin, thickening of the skin or acne like spot, kidney not functioning properly, difficulties in breathing and hydrocephalus which is fluid buildup on the brain. These problems might range from mild to severe and affect each individual differently (Islam & Roach, 2015).

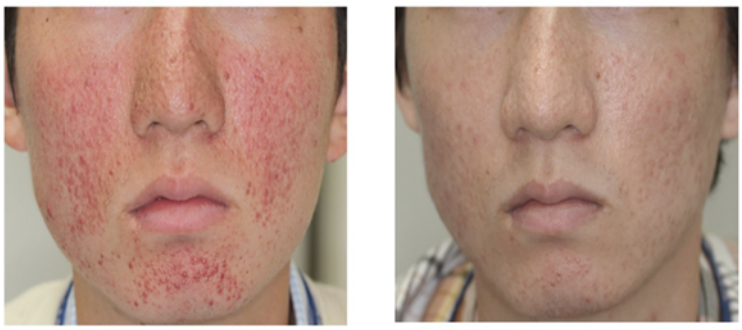

Figure 3.1: Acne like spots seen in TSC (Islam & Roach, 2015).

Probable Causes

Mutations in TSC1 and TSC2 gene are the possible causes of TSC. These genes are engaged in the regulation of cell growth and so the mutation of these genes leads to the formation of the benign tumor in different parts of the body. TSC1/2 gene regulates the phosphoinositide 3-kinase signaling pathway. It inhibits the mammalian target of rapamycin (mTOR) by activating GTPase activity of Rheb. Therefore, mutation in the gene interferes with the inhibitory function of hamartin/tuberin complex. This leads to the phosphorylation of the downstream effector of mTOR and results in uncontrolled growth of cell (Islam & Roach, 2015).

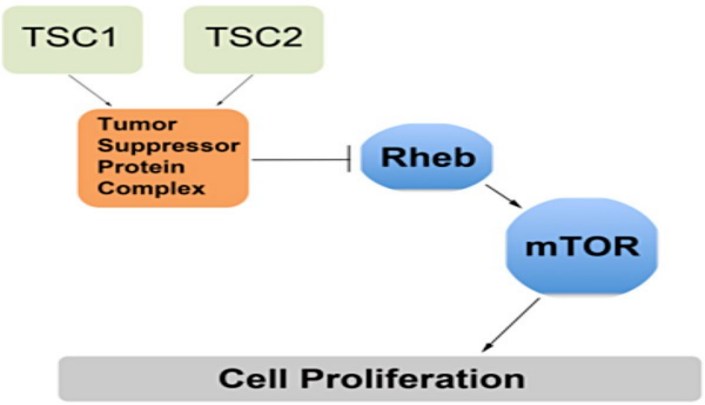

Figure 3.2: Mutation in TSC gene leads to cell proliferation (Islam & Roach, 2015).

Treatment

Apparently, there is no such treatment to treat the TSC directly but the symptoms and conditions can be improved to lead a proper life. For instance, epilepsy can be suppressed using medications. Children with intellectual disabilities can be helped by the extra educational support, ASD depression can be managed by behavioral interventions. Moreover, surgery and medication can be used to remove the tumor, laser therapy can be used for the facial rashes and kidney and lung functions can be restored by medication. Recently, mTOR inhibitor shows light in the path of future treatment for TSC which interfere with the chemical reactions needed for tumor growth (Hasbani & Crino, 2018).

3.6.3: Sleep Problem

About 44 to 83% children having ASD experience sleep problem as a comorbid condition. They face difficulty to fall asleep and sometimes experience disturbance while

sleeping. This condition exacerbates other syndromic forms associated with ASD such as hyperactivity, aggression and attention deficiency. Reports show that about 2-3% children having autism also have sleep issues with a prevalence rate ranging from 54-83% (Xianchen et al., 2006)

Symptoms

common sleep issues are- sleep- onset insomnia (having difficulty to fall asleep), sleep apnea (stops breathing during sleep), sleep walking, night terrors, rhythmic movement disorder (episode of body and head rocking for less than 15 minutes while sleeping), restless leg syndrome and hypersomnia (Kodak & Piazza, 2008)

Probable Cause

A couple of matter can cause such condition in ASD. These are-

- Production of abnormal melatonin: Autistic children have an abnormal level of tryptophan production. It is an amino acid for melatonin production- the sleep regulating hormone. So, their melatonin level fluctuates a lot- higher at daytime and lower at night causing difficulty in falling asleep.
- Heightened sensitivity: It is the reason for the restless brain not being able to calm down enough for an autistic child to fall asleep. They are easily roused by external stimuli such as walking, mosquitos, snoring etc.
- Genetic abnormalities**:** Neurotransmitter abnormalities can lead to reduce the time in REM sleep, the stage where people normally have dream and gives the brain the chance to process memories and learning. Moreover, current researches show that a single gene mutation can lead to insomnia and ASD at the same time (Amanda, Richdale & Schrec, 2009).

Treatment

Bedtime scheduling could be an effective treatment for the sleep problem in ASD children. It involves putting the child to bed and providing naps every night at the same time, and also, awakening the child every morning at the same. This advice seems onerous for the parents to hear if their child is having insufficient sleep. But awakening at the same time every morning is equally important. Extinction therapy can be effective

if used correctly, otherwise it can show a deleterious effect. It involves allowing the child to cry. It can reduce bedtime tantrums. Finally, chronotherapy is a treatment used for adults with sleep disorders but also can be useful for children with autism. It involves putting the child to bed when he/ she is likely to fall asleep rapidly. Then each subsequent night, the time is delayed by 2 hours. It is continued until the acceptable time for their sleep it achieved (Kodak & Piazza, 2008). Many researches have been done on various aspects of sleep problem observed in ASD patient. Some of those research articles' findings have been summarized in the following table 3.2.

Table 3.2: Article summary on ASD children having sleep problem

Research question	Age & number of participants	Measures used	Outcome
To investigate the connection between children's behavioral problem in ASD and sleep problems.	2–18 years & 1784 participants	Children's Sleep Habits Questionnaire and Parental Concerns Questionnaire	Poor sleepers are more prone to behavioral problem than good sleepers (Goldman et al., 2011).
To investigate variables related to sleep problem in children with ASD.	1–15 years & 477 participants	Pediatric Behavior Scale	The strongest predictors of sleep disturbance were autism severity, hyperactivity, mood variability and aggression (Mayes and Calhoun, 2009).
To explore the connection between sleep difficulties and diurnal actions in ASD.	3–14 years & 67 participants (31 kids with ASD and 36 members in control set of	Sleep Diary	Toddlers with ASD are happened to fall asleep late, have extended sleep latencies, spend a major period

	group)		awaking at the night, when results were compared to controls. Those with ASD showed ominously more tough daytime actions than controls (Patzold et al., 1998).
To observe stress, behavioral difficulties and sleep problem in toddlers with intellectual disability (ID).	2–19 years & 77 participants (52 with ID, 7 of which had ASD and 25 in control group)	Sleep Problems Questionnaire	Sleep difficulties were suggestively related with intensity and incidence of Stress and the occurrence of problem difficulties (Richdale et al., 2000).
To explore the connection between sleep, anxiety and ASD.	5–18 years & 187 participants	Children ‘s Sleep Habits Questionnaire	Sleep difficulties and anxiety problem are responsible for 42% of the variance happened in challenging behavior (Rzepecka et al., 2011).
To inspect the connection between sleep difficulties and signs of autism.	5–12 years & 55 participants	Behavior Evaluation of Disorders of Sleep	Less periods of sleeping time each night expected to increase the autism severity and social

			abilities deficits (Schreck, Mulick, et al., 2004).
To compare sleep difficulties in ASD, ADHD and epilepsy.	6–17 years & 256 participants	Sleep Habits Questionnaire	There was an improved risk of sleep problems in kids with ASD and ADHD (Tsai et al., 2012).

(Matson & Goldin, 2013)

3.6.4. Gastrointestinal Dysfunction

ASD children experience different gastrointestinal conditions, possibly due to shared pathogenetic factor as well as pathophysiologic mechanism leading to chronic constipation and abdominal pain. Moreover, diarrhoea and faecal incontinence are highly observed along with stomach bloating and gastro-oesophageal reflux disease (GORD)

Symptoms

The frequency rate of GI dysfunction comorbidity with ASD children ranges between from 9% to 84%. The percentage depends on the method studies that include retrospective studies and prospective studies. Symptoms of GI dysfunction include- intestinal gases overproduction, diarrhea, constipation, gastroesophageal reflux, abdominal pain, bloating etc (Wasilewska & Klukowski, 2015)

Probable Causes

The homology between the gut–blood barrier and blood–brain barrier can be considered for the reason of gastrointestinal (GI) dysfunction in ASD children. There is a close similarity between the GBB- gut blood barrier and BBB- blood brain barrier. This homology can play an important role in the gut- brain communication. As we know the BBB is a selectively permeable barrier, it separates the circulating blood from extracellular fluid in the central nervous system. Thus, it plays a significant role in their communication. In not only function but also anatomically BBB and GBB are analogous.

Anatomically they have many features in common such as they are formed from the endothelial cells of the brain and they are connected through tight junctions. Their homology also includes the increase in permeability due to the activity of the inflammatory mediators such as cytokines, tumor necrosis cells etc. Any disruption in this integrity leads the BBB allowing the leukocytes and neurotoxins to enter the brain. Moreover, the bacterial toxins and neurotropic viruses producing in the intestine may reach the central nervous system through the enteroendrocrine cells or directly through the vagus nerve that has the function to innervate the distal section of the small intestine. Therefore, this can be considered as the reason for GI dysfunction and ASD to result concurrently (Hsiao, 2014).

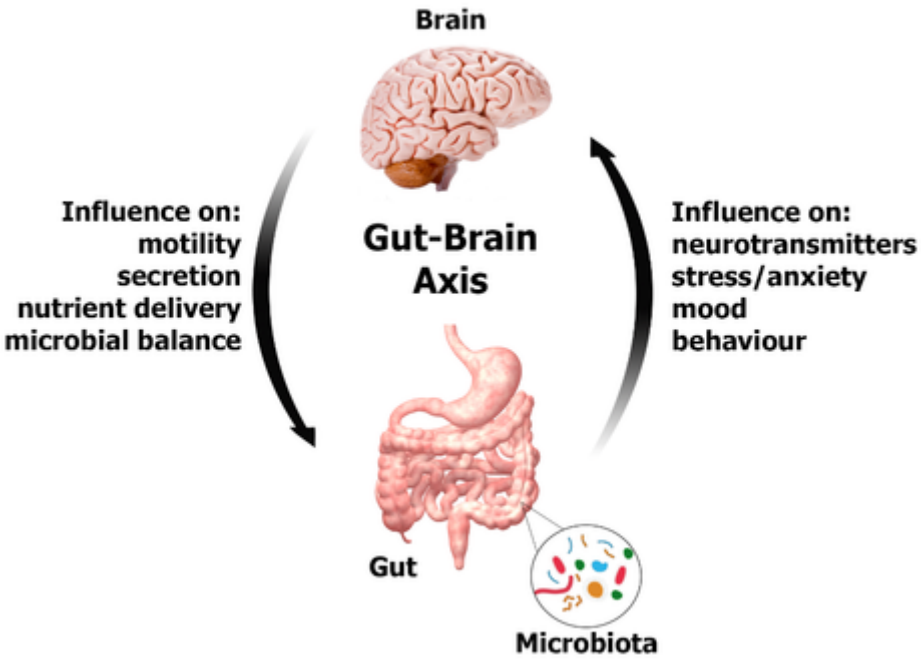

Figure 3.3: Functional relation between GBB and BBB (Hsiao, 2014).

Treatment

There is no recommended medication for the GI problems in ASD children. Medication can only be allowed under critical condition with the close supervision of the physician. However, maintaining the diet can play an important role in improving the life standard of the ASD children.

Diet quality is reflected by the biological activity in the gut ecosystem. This plays an important role for the microbial diversity through its establishment, maintenance and

maturation. The interaction among the microbiome, dietary intake and intestinal epithelial barrier modulate one another. So, dietary intervention can reduce the clinical symptoms in children with ASD. Therefore, parents are encouraged to test different diets such as casein-free, gluten-free [CFGF] diet (Kang, Wagner & Ming, 2014).

Gastrointestinal dysfunction is a serious issue and observed very often in autism. So lately, a lot studies have been done on GI dysfunction and its various aspects. The following table 3.3 contains the summary of different articles' results on gastrointestinal symptoms and dysfunction observed in ASD patients.

Table 3.3: Articles summary on ASD children having gastrointestinal dysfunction

Research question	Age & number of participants	Measures used	Outcome
Compared among 3 groups: (1) people with ASD+GI symptoms, (2) people with ASD but no GI symptoms and (3) people with GI symptoms only.	5–17 years & 121 participants	Clinical evaluation by pediatric gastroenterologists and Questionnaire on Pediatric Gastrointestinal Symptoms	Constipation was found to be the most common GI symptom in ASD patients. It was seen predominantly in younger age (Gorrindo et al., 2012).
Observed the occurrence of regressive autism and related demographic, developmental and medical factors.	2–5 years & 333 participants	Gastrointestinal history form and Sleep history form	No statistically major variances were seen among children with and without regression in case of gastrointestinal indications, past history of sleep problems or

			seizures (Hansen et al., 2008).
Compared toddlers with ASD and gastrointestinal symptoms.	18 years & 363 participants	Medical records	No vital link found amongst ASD and GI symptoms, but for constipation that occur mostly in children with ASD (Ibrahim et al., 2009).
Examined the link between GI indications and depression.	2–17 years & 2973 participants	GI symptom inventory questionnaire	Toddlers with every sort of GI symptom had pointedly greater degrees of nervousness and depression (Mazurek et al., 2013).
Examined the occurrence of GI indications and signs in toddlers with ASD.	24–96 months & 137 participants	Medical records	Twenty-four percentages of toddlers had a past history of one or more GI symptom. No connection was seen amongst GI symptoms and developing deterioration (Molloy and Manning-Courtney, 2003).

Assessed GI symptoms in toddlers with persistent progressive disorders.	5–17 years & 172 participants	Medical history and Side Effects Review Form.	Folks with GI issues were no dissimilar from those who do not have GI symptoms in case of developing functioning or severity of autism symptom. Individuals with GI symptoms presented superior irritability, social withdrawal and anxiety (Nikolov et al., 2009).
Explored GI symptoms and linguistic recession.	1–18 years & 100 participants	The Gastrointestinal Interview	Kids with linguistic regression had been seen having more GI problems (Valicenti-McDermott et al., 2008).
Compared children having ASD to their siblings to show relation between ASD and GI symptoms.	1–18 years & 752 participants	Structured medical history interview	Higher GI symptoms in toddlers with ASD compared to their normally developing siblings (Wang et al., 2011).

(Matson & Goldin, 2013)

3.6.5. Fragile X syndrome

Learning disability may be considered as one of the most common symptoms in ASD children. But this can be caused from another syndrome co- occurring with autism- fragile X syndrome. It is a genetic condition that results in the developmental problems and cognitive impairment. Fragile X syndrome is seen more in male than in female- an approximate estimation through different studies shows a rate that is- 1 in 4,000 males and 1 in 8,000 females (Won et al., 2017).

Symptoms

This fragile X syndrome affect the individual in their development, delay the development, interfere with the ability to learn and use speech and language. Fragile X syndrome is more common in male and shows mild to moderate intellectual disruption. Children with these symptoms can also suffer from anxiety, fidgeting or other hyperactive behavior. This syndrome can also cause attention deficit disorder that result in the individual being unable to maintain the attention and focusing on a specific task (Kay, Gabreski, Jason & Trplett, 2018). Aside from these, they have some characteristic physical features. These features become more visible with age. These include-

-narrow and long face
-long ears
-eminent jaw line
-prominent forehead
-flexible fingers
-flat feet
-male got their testicle enlarged after puberty (Won et al., 2017).

Probable Cause

It is a genetic disorder, so mutation is associated with this syndrome. FMR1 gene mutation is thought to be the causative risk factor in fragile X syndrome. FMR1 gene is important as it gives instruction to make the FMRP protein. This protein again plays the role of regulating other proteins' production and thus helps in the development of the synapse which is critical for nerve impulse.

Most of the cases with fragile X syndrome show a mutation where the DNA segment- CGG triplet repeat and this results in expansion of the FMR1 gene. This repetition can

occur as mamy as 5 to 40 times. This abnormal expansion of CGG segment causes FMR1 to turn off and interfere with the production of FMRP protein. This disturbs the function of the nervous system and shows the symptoms commonly observed in FXS (Kay, Gabreski, Jason & Trplett, 2018).

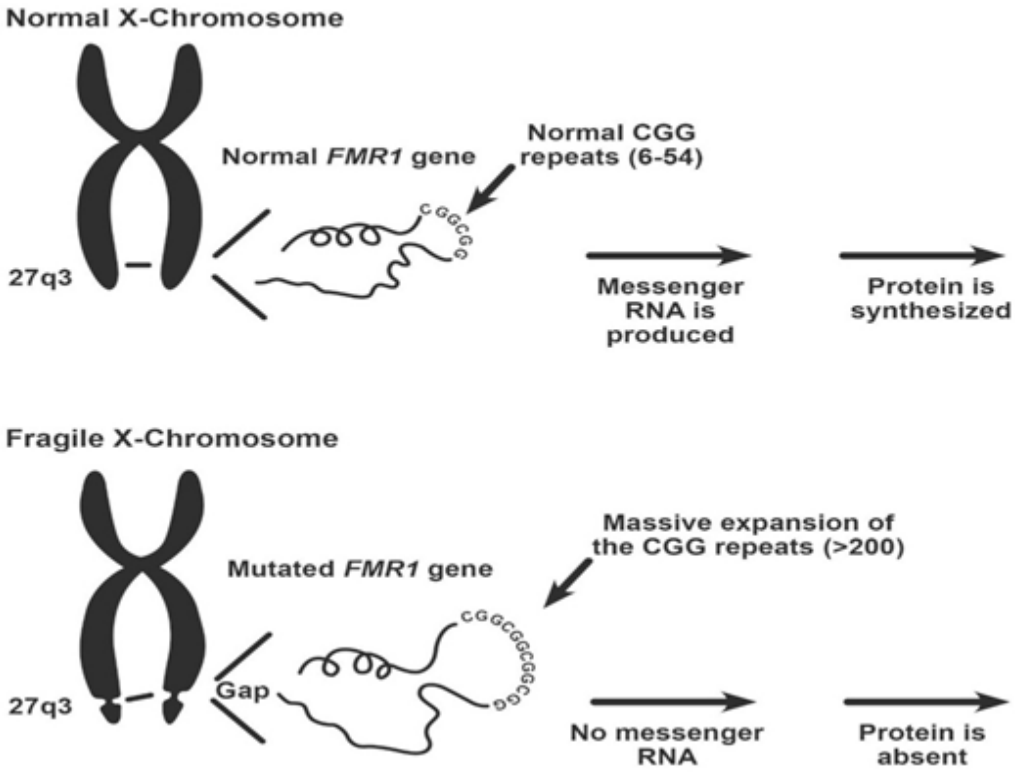

Figure 3.4: Expansion of the CGG repeats in a region on FMR1 gene on X chromosome, resulting in decreased mRNA and FMRP production, leads to Fragile X syndrome (Kay, Gabreski, Jason & Trplett, 2018).

Treatment

To date, no medication has been discovered to cure the fragile X syndrome. Like others, medications can only be allowed to minimize the symptoms observed and maintain life quality. A recent study shows melatonin as a novel intervention for this syndrome (Won et al., 2017).

3.6.6: Attention Deficit Hyperactivity Disorder (ADHD)

Attention-deficit/hyperactivity disorder (ADHD) is considered as a brain disorder characterized by the difficulty for the child to focus and maintain attention on a subject followed by hyperactive impulses. This disturbs the normal functions and development process of the child and it is highly observed in the children diagnosed to have autism. Attention deficiency results in the lack of persistency and difficulty in focusing. Children with this disorder tend to wander off tasks. This condition is not merely because of the lack of comprehension. Hyperactivity results in the inappropriate talks, excessive fidgets. Children tend to move around inconsistently in this disorder. Adults with this condition show extreme level of restlessness. Impulsivity leads to inclination to act on impulse rather than thought making the person with this disorder hasty in their actions. It makes the person to do an action in a moment without thinking first of themselves or others and ultimately cause harm (Santosh et al., 2006).

Symptoms

As the name suggests, Inattention, hyperactivity and impulsivity are the key characteristics observed in ADHD. Some people with ADHD show only one of these three symptoms. But in most of the cases, children with this disorder show more than one symptoms. ADHD co- occurs with ASD and shows potential disturbance in their daily life (Santosh et al., 2006).

Probable Cause

The specific mutated gene in ADHD is not confirmed yet. But researches show that mutation in the glutamate receptor gene family may interfere with the signaling pathway in the brain of the children with ADHD (Nordqvist, 2011).

Another research shows, specifically the mutation in the NMDA receptor 2B subunit gene leading to shorten Grin2b. And this can result in the symptoms commonly seen in the ADHD and ASD. Children with this mutation have relatively smaller anterior

cingulate cortex which is the region of the brain responsible for attention, motivation and recognition.

Not all the children with this disorder show this mutation but majority of the group do. This can pave the path for future research for potential therapy for this disorder (Hu et al., 2016).

Treatment and Therapies

As we know there is no available cure for this disorder, but the current treatments only aim to improve the symptoms associated with this disorder and ASD. These treatments include some medication prescribed by registered physician and psychotherapists. But mostly different management and behavioral therapy are used to improve the condition which aim at improving children's' attention in classroom or other places. (Reiersen & Todd, 2008).

Medication

Medications are used to reduce the symptoms of hyperactivity and impulsivity. Thus it helps to improve their ability to focus on the work and also can improve learning capacity. Medication can also help to improve the co- ordination of the brain. Several different medication and dosage are tried out to find the precision medication for a particular individual, so that has to be supervised by a registered therapist, psychiatrist or physician. Such as- stimulant is often used in this disorder. This may seem unusual to treat a hyperactive condition but specific dose of the stimulant helps in improving thinking and attention by increasing dopamine and norepinephrine. Therefore, close monitoring of the healthcare professional is very crucial in implying medications in this condition. Under supervision, stimulants are considered safe.

But, there are certain risks and side effects, for instance- stimulants increase blood pressure as well as heart rate and so it can lead to increase the anxiety. A person with high blood pressure or seizures cannot be treated with stimulant; this is also applied for the people having heart disease, liver or kidney dysfunction, glaucoma and/ or anxiety disorder (Reiersen & Todd, 2008).

Psychotherapy

Adding psychotherapy has the potential to better the symptoms seen in the ADHD and ASD such as behavioral therapy that helps the person with this disorder to change or at least improve their behavior. It involves practical assistance from organizing different tasks at home and school to finish the homework (Reiersen & Todd, 2008). The following table 3.4 shows different results retrieved from different studies done on ADHD in ASD patients.

Table 3.4: Article summary on ASD children having ADHD

Research question	Age & number of participants	Measures used	Outcome
Explored to see if children with Pervasive Developmental Disorders (PDDs) show symptoms connected to ADHD to permit a comorbid identification of ADHD.	Mean age = 8.5 years & 57 participants	Retrospective chart review and Conner's Parent and Teacher Rating Scales-Revised, Long Version	About 26% of folks with PDDs encountered norms for the shared kind of ADHD, while 33% met norms for the Inattentive type of ADHD (Goldstein and Schwebach, 2004).
To govern the extent to which ADHD and autistic symptoms overlap.	2–16 years & 847 participants with autism; 158 with ADHD	Based on DSM-IV criteria	ADHD signs were very common in autism (Mayes et al., 2012).
To evaluate which kinds of neuro-psychological deficits occur frequently along with ASD and	18+ years & 161 participants	DSM-IV criteria checklist	The dysfunctions of the ASD and comorbid ADHD group cannot be seen as a summary of the dysfunction

ADHD in adults.			found in the ASD and ADHD groups (Nyde´n etal., 2010).
To evaluate and compare executive functioning profiles in children with ADHD and in children with ASD with and without comorbid ADHD.	6-18 years & 80 participants	Examination by an experienced child and adolescent psychiatrist according to DSM-IV-TR criteria	Those with ASD and comorbid AD/HD symptoms showed more problems in inhibitory performance than those with ASD alone (Sinzig et al., 2008)
To inspect patterns of comorbid psychiatric problems in children with ASD and their parents compared to age-matched controls and their parents.	ASD group: Mean = 12.73 years; Control group: Mean = 11.85 years & 134 people (67 in each group)	Child Behavior Checklist 6-18	Almost half (44.78%) of the ASD group met CBCL criteria for clinically significant hyperactivity disorder (Skokauskas and Gallagher, 2012).

(Matson & Goldin, 2013)

3.6.7: Seizure and Epilepsy

Seizure and epilepsy are very common in children. The most common form of seizure is febrile seizure and many children experience this kind of seizure during their early childhood. Epilepsy is simply the result of having unprovoked and recurrent seizures without any exact underlying reason. It is also considered as one of the most common form of chronic neurological disorders. Sometimes the seizures resolve by itself within

one or two years but a lesser percentage of seizure type in epilepsy cannot be controlled by treatment (Frye, 2012).

Symptoms

Seizure is thought to be the main symptom in epilepsy. The symptoms can vary largely depending on the type of seizure and the individual itself. Generalized seizure and partial seizure are the two classes of seizures that are identified.

Partial seizure involves only a specific region in the brain and causes mild to light seizure to the parts of the body that is controlled by the affected area of the brain. It does not result in any loss of consciousness. Tingling and twitching limbs, dizziness and altered taste, smell and sight are the most common symptoms in partial seizure. Generalized seizure, on the other hand, involves the whole brain and mostly causes loss of consciousness. Absence seizure, tonic seizure, atonic seizure, clonic seizure, myoclonic seizure, tonic- clonic seizure- are the types of generalized seizures with characteristic symptoms.

In ASD patient seizure is the most common characteristic symptoms. 5 to 38% of the ASD population suffers from seizure (Scharfman, 2007).

Probable causes

No exact cause of epilepsy is found. However, in a minority of cases some causes are listed, such as, head injuries during birth, brain tumors, infections (meningitis), and stroke etc. Genetic mutation associated with epilepsy has not been seen. But there could be a strong link to genetic mutation with seizure. Seizures result from irregular discharge of electric impulses. Discharge of electric impulses determines the type of seizures. When discharge involves a specific region of the brain and does not spread the neighboring areas, this results in partial seizures. In generalized seizure, electrical discharge spread whole brain. This results in convulsion of the muscles controlled by the affected region of the brain (Scharfman, 2007).

Diagnosis of seizures in children with ASD

In normal cases a person experiencing seizure is very easy to identify. However, in case of ASD, it is equally difficult to differentiate the seizures from abnormal behaviors. For instance, an autistic child often experiences staring episode, stereotyped movement and

motor tics that can be easily confused with the seizure. But it is very important to differentiate abnormal behavior from seizure for the proper treatment or the condition of the patient can deteriorate. Electroencephalogram is the most considerate tool to get an accurate diagnosis in this kind of cases. Electroencephalogram is a method to monitor and record the electrical activity in the brain. So, it can be considered as a form of electrophysiological monitoring (Scharfman, 2007).

Treatment of seizure in case of ASD patient

There is no treatment discovered yet to treat the root cause of epilepsy. Though seizures are mostly treated with antiepileptic drugs (AEDs), in most cases drugs are not prescribed. In case of failure to control the seizure by AED, non AED treatments are followed. There is a wide range of AED but not all are suitable for use when it comes to autistic children as they experience multiple symptoms at the same time. Therefore, a few treatments are specified through various studies and some treatment guides are summarized in table 3.5.

Table 3.5: Treatment guide to select AEDs

A guide to selecting antiepileptic drugs (AEDs).		
ASD Symptoms	Avoid	Possible Alternative
Gastrointestinal Disorders	Valproate	Lamotrigine
Mitochondrial Disorders	Valproate	Levetiracetam, Lamotrigine
Poor growth	Topiramate	Lamotrigine
Overweight	Valproate	Topiramate, Lamotrigine, Levetiracetam
Behavioral problems	Levetiracetam	Lamotrigine, Valproate, Topiramate

(Frye, 2012)

Epileptic condition in ASD children has been studied over the course of time to find different aspects of this co-morbid condition. Sometimes they occur alone in children and sometimes it is associated with autism or other neurological disorder. As we know, there is no medication to treat the underlying cause of autism; it becomes even harder for the doctors and healthcare specialties to treat epilepsy and seizure when it occurs with other conditions. Therefore, it becomes a burning topic and many researches have been done. The result of these researches have been summarized in the table 3.6.

Table 3.6: Article summary on the epileptic condition in ASD children

Research question	Age and number of participants	Measures used	Outcome
To compare epilepsy prevalence in two participants groups (1) those with and without intellectual disability, and (2) males and females with autism.	1–28 years & 2112 participants.	Being a Meta-analysis study a variety of measures had been used in individual studies.	Epileptic condition in autism is highly associated with intellectual disability as well as gender (Amiet et al., 2008).
To carry out a long-term follow up study to identify the characteristic features found in an individual with autism and at the same time correlate the connection between epilepsy and autism.	26–56 years & 150 participants.	Clinical records and semi-structured interview. Electro-cephalogram (EEG) reports are sought by author whenever possible.	There is a strong connection among epilepsy, autism and intellectual disabilities (Bolton et al., 2011).
To address the abnormalities in electroencephalography in children with PDDs.	1–14 years & 56 participants.	Retrospective review of EEG data.	Epilepsy co-occur in 40% children with ASD (Gabis et al., 2005).

To inspect the result of study which demonstrates that seizure disorder has appeared more in children with ASD than in atypically developing toddlers.	18–24 months & 36 participants.	Diagnoses of tics and seizure disorder by the primary care physician.	Children with seizures are more prone to be impaired than those who don't have seizures (Matson et al., 2010).
To run a comparative study between two groups of autistic children those who have epilepsy and those who don't have the condition and see their psychological and developmental functions.	7–17 years and 120 participants.	Previous diagnosis of epilepsy by a medical professional.	Motor difficulties are more prominent in ASD and epilepsy co-morbidity (Turk et al., 2009).
To compare behavior difficulties among 3 groups: (1) individual with Epilepsy; (2) with ASD and (3) ASD + epilepsy.	29–72 years & 100 participants (25 in each group)	Medical explanation of seizure activity. Accessible medical evidence (for instance, family history, onset age, previous neurological trauma)	Individuals with ASD and epilepsy were more prone to be impaired than those who have either ASD or epilepsy (Smith and Matson, 2010).

(Matson & Goldin, 2013)

Chapter 4: Conclusion

As we have known that the term ASD act as an umbrella to shade different co-morbid conditions at the same time. The comorbid conditions associated with ASD results from different gene mutations, hormonal imbalance or neurotransmitters dysfunction. They can occur alone but in a patient with ASD their chances to occur in that patient is very high. This condition of co- morbidity makes the autism very heterogeneous. The heterogeneity in the ASD makes it difficult for the physician to treat the autistic person. Most accepted theory for this reason is that co-occurrence makes it more difficult to diagnose the conditions at the same time. Differentiation among symptoms become also very challenging. For example, seizure is observed both in epilepsy and tic Disorders. But their treatment path is different. Therefore, differentiation among symptoms is very important. Moreover, medication for one symptom can sometimes worsen the condition of other symptoms. And the challenges faced by the families and the individual itself are beyond description.

Pharmacological treatment can be considered of a great significant in the improvement of the functioning of the children with autism. It can also help decrease the child impairment and pave the way for their proper social and mental development. Mostly, it will be beneficial when the severity of symptoms and co- occurrence of multiple conditions make it difficult for the child with autism to participate in traditional therapy to suppress the symptoms. Individual medicine treatments and integrated multimodal approach should be considered due to the clinical heterogeneity. So precision in the medication therapy is the new era of the research in ASD. An autistic child with ADHD and other autistic child with intellectual disability will need different medications thought the symptoms are quite similar. Medication also depends on other health conditions and individual requirements. For example, one child with hyperactivity cannot be treated with beta blocker anti-hypertensive drugs if he/ she have been suffering from asthma.

Though most of the studies target suppressing the symptom, there remains a challenge to compare and justify different treatment efficacy in both neurotypical and ASD groups with different co- morbid conditions. In ASD, abnormal neurochemical signals result in the impairment of social and physical development. Therefore, selective pharmacological intervention targeting on specific neurobiological pathways can lead to a wide

opportunity in improving clinical features. For instance, autism related stereotype behaviors can be controlled by mediating bGABAergic signaling. However, it varies from person to person and depends on the severity of the co morbidity. Individualized treatment with oxytocin may have a milestone result in improving social interaction and emotional development.

Therapy and medication or pharmacological approach has not been able to eliminate the root cause of ASD. Still the most accepted theory of the cause of autism is gene mutation, so gene therapy would be the best possible way to treat the root cause of autism. Gene therapy can really change the scenario by correcting the mutated DNA sequence. Here, the challenge is to identify the involved culprit gene which can be done by using stem cell. So, stem cells are also giving hope to eliminate the problems associated with gene therapy. Therefore, a lot of research is needed.

Individualized treatment is the best option in any kind of treatment to avoid the risks that might arise from co-morbid conditions and other factors. Moreover, lack of research, selection of medication, long-term prognosis, stress and burden to care providers make it important to study co-morbidity in autism. Lastly, autism prevalence rate being so high is really hindering the progress of a nation. However, these children and young adults can really be trained properly to make a turning point in this situation. The researches on autism have to be fastened to find out proper and precision treatment for these conditions.

4.1: Limitations of the study

Sometimes information collection was relied on the materials that are likely to be out of date. On the other hand, there were also some articles containing a lot of information on different symptoms of autism. But as those articles failed to differentiate among those symptoms from the co-morbid conditions, they had to be overlooked.

4.2: Recommendations for future research

Future researches could be done on gene therapy treatment, its application, limitation and stem cell technology etc. These are the future fields for researches on ASD and its co-morbid conditions.

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