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Autism Spectrum Disorder: A multifactorial analysis of genetics, early diagnosis and treatment to achieve the optimal outcome

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Abstract

Autism Spectrum Disorder (ASD) is a neurodevelopmental disease that impacts 1 in 54 children in the United States. Generally, the associated symptoms of ASD include social and communication impairment, intellectual disability, and repeated rigid movements. ASD encompasses many different characteristics and different standards of diagnosis. It is complicated because it is characterized as a spectrum disorder - it could range from very severe cases to mild cases of this disorder. Along with *Attention Deficit Hyperactivity Disorder*, ASD is ranked as the most common neurodevelopmental disorder. What complicates this disorder even further is that there are over 100 genes associated with ASD, although these genes differ for each patient. Moreover, because of genetic variability, there is a lack of standardized diagnosing protocol for ASD. The life-long symptoms of ASD makes those with this disorder suffer greatly because in most cases the symptoms do not get reduced and ASD patients do not "grow out of it". However, there is a primary goal for those with ASD to have reduced symptoms or no symptoms at all which is known as *optimal outcome* - the ultimate goal for those with ASD. This phenomenon is directly linked to earlier intervention, because of the greater plasticity of the brain at a younger age, which is linked to diagnosis. There are two primary routes of diagnosis - quantitative and qualitative measures. The *Social Response Scale* (SRS) is a commonly used and validated quantitative test to diagnose ASD. The qualitative measure is from the perspective of a parent or a physician where they assess the symptoms associated with ASD - lack of communication skills, lower intellectual ability, and repeated rigid movements. Although the genetic component of ASD is very complex, finding a genetic mechanism would make early diagnosis easier and the subsequent initiation of early specific intervention could lead to optimal outcome for ASD patients.

Keywords: Autism Spectrum Disorder, Attention Deficit Hyperactivity Disorder, Optimal Outcome, Social Response Scale, Quantitative, Qualitative, Early Intervention, Genetics, Diagnosis, Plasticity

1. Introduction

Autism Spectrum Disorder, a neurodevelopmental disease consisting of a group of complex neurodevelopmental disorders that are represented by social impairment and repetitive behaviors. Though the time when ASD symptoms become visible vary, there are some cases where the child develops normally but starts to show symptoms at age 2 or 3 years old (*Autism Spectrum Disorder Fact Sheet*, n.d.). While there are disorders related to ASD ranging from Fragile X Syndrome to tuberous sclerosis, there is no definitive known root cause to

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ASD. In past years, there have been many developments with regards to increasing the quality of life of those with ASD. Though ASD is often considered a lifelong disorder, there is a group of individuals who lose some or all of their symptoms. This characteristic is classified as the optimal outcome. This characteristic is measured by utilizing a scale to rate qualitative characteristics ranging from visual reception to communication and socialization. The main objective was that with a comprehensive behavioral and developmental plan at an earlier age, consisting of intervention from trained therapists and clinicians, would enable the symptoms of children with ASD to improve and increase their chances of becoming healthier or achieving the optimal outcome. The two possible outcomes of the randomized control trial that was conducted to test the efficiency of the ESDM, was an improvement in symptoms or a decline in symptoms which was run utilizing screening examinations, to find a qualitative measure and compared to their initial scores. This review aims to investigate the correlations of genetics, early diagnosis and comprehensive intervention on the possibility of achieving the optimal outcome.

2. Genetics of ASD

Genetics plays an imperative role in ASD. There are around 100 genes associated with ASD and it differs in each patient, demonstrating how difficult it is to diagnose ASD definitively. Moreover, ASD is not associated with a single gene. It is not only the number of genes that cause this issue, but also that these genes only account for some of the total ASD cases, but not all of them. As a spectrum-disorder, ASD has a varying level of severity due to different amounts of genes with mutations. This paper will highlight two genes, *Phosphatase and tensin homolog* (PTEN) and *tuberous sclerosis complex 1 and 2* (TSC1/TSC2) that have shown to be associated with ASD.

According to the Brain Facts Book, PTEN is a tumor suppressor enzyme that controls cell division and prevents uncontrolled cellular proliferation. It also activates the mTOR pathway through its repression of several intermediate proteins (Figure 1). The *mTOR pathway* is a significant part of cell proliferation and growth - it monitors "the availability of nutrients, mitogenic signals and cellular energy and oxygen levels" (Zarogoulidis, et al., 2014). If PTEN mutations, such as PTEN haploinsufficiency, are what primarily cause ASD, a potential solution is inhibiting the mTOR pathway (Sato, 2016). To test this theory, scientists have conducted studies with mice who have PTEN mutations. PTEN-mutant mice had altered sociability, anxiety, and repetitive behaviors. Scientists used drugs that inhibit the mTOR pathway (Wnuk, et al., 2018). The mice's anxiety, social, and communication skills markedly increased after treatment, thus resulting in an improvement in quality of life (Sato, 2016). These results indicate the potential cause and treatment for those with ASD. Taken together, these results suggest that inhibiting the mTOR pathway and its rapid cell proliferation and growth could be a possible factor in improving ASD symptoms.

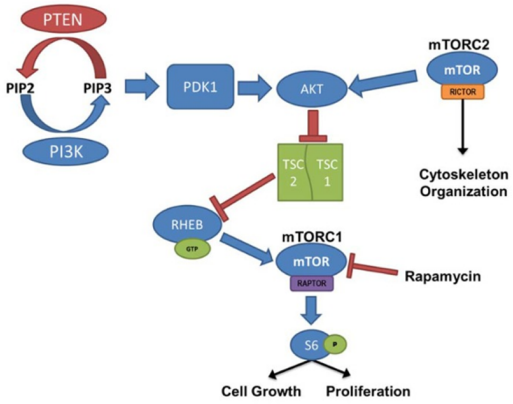

Figure 1. *P13K-PTEN-mTOR Pathway*. The figure shows how PTEN and TSC1/2 are upstream modulators of the mTOR pathway. Activation of the mTOR pathway leads to effects downstream in cell growth and proliferation (Lasarge & Danzer, 2014).

In addition, TSC1 and TSC2 are also associated genes with ASD. TSC1 and TSC2 are genes that code for proteins that control cell growth and size. A mutation on TSC1 and TSC2 causes tuberous sclerosis, which is characterized by uncontrollable cell growth, which could lead to numerous benign tumors in the body. (*Tuberous Sclerosis Complex*,

2020). Interestingly, 40% of patients with tuberous sclerosis also have ASD, demonstrating the possibility of a similar genetic cause. Contributing to the mTOR pathway, these genes have a major role in terms of cell growth, metabolism and proliferation (Wnuk, et al., 2018). This once again shows the correlation between the mTOR pathway and ASD, which can provide a different outlook on the cause of autism. If a genetic characteristic of autism was discovered, early diagnosis would become possible similar to the means of diagnosing disorders like Down-syndrome, which is associated with Trisomy 21. The identification of a trisomy 21 immediately dictates that Down syndrome is present, demonstrating how it could be diagnosed easily.

Although PTEN and TSC1/TSC2 are important for the development of ASD, twin studies now show that genetics may not be the only factor in developing ASD. Some people are more prone to ASD than others. If one twin were diagnosed with ASD, the other twin is only 36-95% likely to be diagnosed as well (Autism Spectrum Disorder Fact Sheet, n.d.). Identical twins have the same genetic makeup so one would assume the genetic heritability is 100%, which is not the case here. This suggests that there may be other epigenetic factors that contribute to ASD development. These questions can only be answered with further research in this field. Because the genetic makeup of identical twins are the same, the fact that the other twin is not guaranteed to have ASD shows that genetics is not the only factor in play, which once again describes the complexity of diagnosis.

3. Quantitative and Qualitative Diagnostic Measures

ASD is diagnosed with both qualitative and quantitative measures. The qualitative measure is usually done by the parents or pediatricians who screen for the associated symptoms of ASD, including lack of communication skills, lower intellectual ability, and repeated rigid movements. There are three types of tests that screen for ASD in a quantitative manner. The Social Communication Questionnaire (SCQ) and the Social Responsiveness Scales (SRS) are easy and inexpensive ways to screen for ASD routinely. The Autism Diagnostic Observation Schedule (ADOS) is another quantitative test that is conducted by a trained-physician.

The SCQ is a questionnaire type test. It was created for children 4 years and older, who have a mental age above 2. Mental age is defined as a combination of factors including responsibility, IQ, and social skills at a specific time. The time duration assigned to complete the assessment is 10 minutes. The SCQ is to be completed by either the parent or caregiver and consists of 40 yes-or-no questions. An example of a question is “gets hyperactive, angry, screams, yells often” and the parents would have to answer true or false for this question (Social Communication Questionnaire: Questions, General Description, Uses and Limitations, 2019). The assessment measures the communication and social skills from a parent/caregiver standpoint. This questionnaire utilizes the qualitative symptoms observed by parents to provide the predicted severity of each symptom, thus providing a diagnosis if the cutoff score meets the limit needed for ASD. There are two versions of this specific assessment - Lifetime and Current (Rutter, 2003). The Lifetime SCQ assessment utilizes the child’s complete developmental history. The cutoff score for a probable diagnosis of ASD on this type is 15 where the possible score can range from 0-40. The Current SCQ assessment utilizes the child’s developmental history for the past 3 months and is used to determine improvements or worsening of ASD symptoms.

The SRS is also a questionnaire type test. The second edition SRS assessment consists of 4 different types of forms - a school age form, a preschool form, an adult (relative/other report) form, and an adult (self-report) form (Social Responsiveness Scale, Second Edition (SRS-2), n.d.). The school age form is created for children of ages 4 to 18 and should be completed by a parent/caretaker. The preschool form is created for children of ages 2.5 to 4.5 and should be completed by a parents/caretaker as well. The adult (relative/other report) form is for ages 19 and up and should be completed by a relative or guardian. The adult (self-report) form is for ages 19 and up and should be completed by the adult themselves. The time duration to complete the assessment is 15 to 20

minutes, which is longer than the SCQ assessment. The SRS reveals aspects of social skills that are usually missed by parents/caregivers - the yes-or-no questions are key for this principle (Moody, et al., 2017). Social awareness, social cognition, social communication, social motivation, and restricted interests and repetitive behaviors are the five subscales in which the severity and social deficits are portrayed by the total score (Social Responsiveness Scale, Second Edition (SRS-2), n.d.).The aggregate of all five subscales determines the severity of ASD symptoms. The score for the SRS ranges from 15 to 60. 30 is the cut-off score on this assessment where a score in the range 30-36 results in the diagnosis of mild/moderate autism, a score greater than 37 is classified as severe autism and a score below 30 is classified as no autism (Park, et al., 2018). Some limitations of self report tests are confirmation and observer bias. For example, if a person is filling out the SRS questionnaire for themselves or for their child and firmly believes that they have ASD, due to confirmation bias, they are more likely to answer yes to some questions. Confirmation bias is the tendency to interpret evidence or answer questions as a way to confirm one's existing beliefs (Nickerson, 1998). Observer bias is a discrepancy that is caused during the process of observing or recording information (Mahtani, et al., 2018). Confirmation and observer bias could potentially skew the results of the questionnaire, thus affecting the patient's official score and diagnosis.

Another diagnostic measure that is more accurate than SCQ and SRS is the ADOS test. It is an activity-based assessment done by trained clinicians who utilize controlled scenarios and makes direct observations about the patient's behaviors. Clinicians are paired with individuals who they have no relationship with. (Dreison, 2019). The ADOS test can be done for 12-month infants and older and usually takes 30-60 minutes to administer. It consists of direct observation of the symptoms present as well as interviews with the individual and possibly the individual's parents (Dreison, 2019). Confirmation and observer bias is reduced because a team of trained clinicians review a video recording to make a diagnosis. It also takes around 1-2 weeks to receive the results. Although the ADOS test takes more time, there is less bias because it is conducted by trained clinicians.

These quantitative methods - SCQ, SRS, and ADOS - use subjective observations of symptoms in children to make a diagnosis. However, there is currently no pure quantitative test that does not revolve around the symptomatic basis of ASD. If such a source for diagnosis were available, this would mean a more definitive diagnosis for ASD, which would reduce the bias sometimes produced by SCQ and SRS. SRS, SCQ, and ADOS assessments remain an effective mechanism to screen for ASD, however, there are limitations. Therefore, if there existed a quantitative diagnostic, that would be more beneficial for early intervention, which would yield a higher probability for an optimal outcome.

4. The Benefits of Early Intervention and Connection to Optimal Outcome

Some studies have demonstrated that early intervention is primarily what increases the chances of achieving an optimal outcome. One such early intervention that was used in a randomized-controlled trial was the Early Start Denver Model (ESDM). The ESDM was a comprehensive developmental behavioral intervention that was delivered by trained therapists and parents for 2 years. (Dawson, et al., 2010). 48 children with ASD who were 18-30 months old were randomly assigned to one of two groups, the one that used the ESDM, or the assess and monitor group (A/M). In the A/M the child was referred to a local provider that provided intervention that is commonly provided in the community. (Dawson, et al., 2010). The A/M group got yearly assessments with recommendations on possible interventions as well as referrals for intervention from community providers in the region. The ESDM group received yearly assessments, 20 hours a week of the ESDM intervention from clinicians, parent training, and parent administration of the intervention for 5 or more hours per week (Dawson, et al., 2010).

The results of these trials after 2 years were significant improvements in IQ, adaptive behavior, and autism diagnosis for the ESDM group when compared to the A/M group. In addition, the ESDM

group displayed a 17.6 point improvement in their ADOS score collected at both the beginning and end of the trial, while those in the A/M group displayed an average of 7.0 point improvement. This demonstrates that when compared to "average" intervention, the ESDM group had more of a positive impact for those with ASD proving that it is more effective in this trial. The study also highlighted the importance of an early and comprehensive developmental behavioral intervention, as evidenced by improvements in IQ, adaptive behavior, and ASD diagnosis after the 2 years of the trial. The A/M community intervention represents a normal intervention program that most people diagnosed with ASD would likely get. The difference in effectiveness between the ESDM and the community intervention shows that initiating interventions at an earlier stage that is more specific to the symptoms exhibited seems to reduce the severity of ASD and produce long-term results. It brings them closer to the ultimate goal of optimal outcome.

There primarily seems to be a correlation between early, focused intervention and optimal outcome. When there is early intervention, this is caused directly because of early diagnosis. If intervention is started early, the child's brain is more "'plastic' or changeable" giving children the best chances to develop to a greater level. This characteristic makes it easier to improve based on treatment plans like behavioral and speech therapy at younger ages, relating to the direct correlation between early intervention and optimal outcome (*Early Intervention for Autism*, n.d.). In some cases, this means losing all the symptoms associated with ASD and having a tremendous improvement in both IQ and adaptive behavior as well as social skills like communication. However, most often, an improvement in IQ, social skills, adaptive behavior, and ASD diagnosis is associated with reduced symptoms translating to an optimal outcome (Fein, et al., 2013). This demonstrates the associated relationship between early, focused interventions and an increased chance of achieving an optimal outcome.

5. Conclusion

There are many diagnostic measures and interventions present for diagnosing and treating the symptoms of ASD. The current diagnostic methods are usually based on qualitative measures as well as quantitative measures that primarily analyze the symptoms present. As discussed in this paper, the genetics behind ASD is very complex and there are over 100 genes associated with the disease. Finding a genetic mechanism instead of a gene that contributes to ASD would facilitate the creation of a definitive diagnostic measure. Through analysis of different interventions such as the ESDM intervention that was composed of highly specific behavioral therapy, it was observed that early specific intervention tends to increase the chances for optimal outcome. The combination of definitive diagnosis as well as early specific intervention correlates with optimal outcome in those with ASD.

Overall, there are many areas for research in ASD. One of the main things that researchers should focus on is finding a genetic mechanism or an "identifying factor" that correlates to ASD. Identifying a mechanism would contribute to a faster and more definitive form of ASD diagnosis. Diagnosing ASD at an earlier stage leads to earlier intervention for children, thus increasing the chances for optimal outcome. Furthermore, another area which requires development is the creation of patient-specific treatment for those diagnosed with ASD. By doing so, there would be a patient-specific treatment plan that would be followed which would help reduce the severity of the symptoms and increase the chances of optimal outcome. Throughout the years, the quality of life of those with ASD has improved greatly and with continued advancement more developments are to come for those with ASD.

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