Epidemiology of autism in Georgia and predictors of optimal outcome.

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As the author of the submitted dissertation, I declare that this thesis is wholly my own work unless otherwise referenced or acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis. This document has not been submitted for qualifications at any other academic institution.

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აბსტრაქტი

შესავალი

აუტიზმის სპექტრის აშლილობა მიეკუთვნება (ასა) ნეიროგანვითარებით დარღვევებს და ხასიათდება სოციალური კომუნიკაციისა, გაღარიბებული ინტერესების და ქცევის სირთულეებით, რაც გრძელდება მთელი ცხოვრების განმავლობაში. ასა-ს გამოსავალი სხვადასხვა შემთხვევაში განსხვავებულია - შესაძლებლობების მძიმე შეზღუდვიდან ასა-ს სიმპტომების მნიშვნელოვან შემცირებასა და თითქმის ტიპურ ფუნქციონირებამდე. ამ უკანასკნელ შემთხვევებში საუბრობენ ასა-ს ოპტიმალურ გამოსავალზე (ოგ).

კვლევის მიზანი

კვლევის მიზანი იყო ასა-ის გავრცელების შეფასება, მისი კლინიკური მახასიათებლების იდენტიფიცირება და შესაძლო ოპტიმალური გამოსავლის პრედიქტორების გამოვლენა.

მეთოდები

კვლევა იყო პროსპექტულ-კოჰორტული, რომელიც ჩატარდა სამ ეტაპად: სკრინინგი, დიაგნოსტიკური შეფასება და განმეორებითი შეფასება. კვლევის პირველ ეტაპზე სამიზნე პოპულაცია იყო თბილისის პირველადი ჯანდაცვის ცენტრებში რეგისტრირებული 2-დან 4 წლამდე ასაკის ყველა (2651) ბავშვი. სკრინინგი გაიარა მათმა 77.1%-მა (2044) ასაკისა და ეტაპების კითხვარით (ASQ) და აუტიზმის მოდიფიცირებული საკონტროლო კითხვარით პატარა ბავშვებისთვის (M-CHAT).

მეორე ეტაპზე რისკის ჯგუფის ბავშვები დიაგნოსტიკურად შეფასდნენ: აუტიზმის დიაგნოსტიკური დაკვირვების სქემით (ADOS), აუტიზმის დიაგნოსტიკური ინტერვიუთი (ADI-R) და ვაინლენდის ადაპტური ქცევის სკალით (Vineland II). საბოლოო დიაგნოზის ფორმულირება მოხდა მულტიდისციპლინურმა გუნდის შეფასების და განსჯის საფუძველზე.

მესამე ეტაპზე გაგრძელდა მონიტორინგი 44 ბავშვზე, რომელთაც დაესვათ აუტიზმის სპექტრის აშლილობის დიაგნოზი. 36 თვის განმავლობაში დაკვირვება ხდებოდა ბავშვების სოციალურ-კომუნიკაციურ უნარებზე. ამ ხნის განმავლობაში ყველა მათგანი იღებდა ერთიდაიგივე ტიპის და ინტენსივობის ინტერვენციას - გამოყენებითი ქცევითი ანალიზზე დაფუძნებულ (ABA) თერაპიას, სიხშირით ხუთი

ერთსაათიანი სესია კვირაში. ოპტიმალური გამოსავალი (OO) განისაზღვრა, როგორც ასა-ს სიმპტომების კრიტიკული გაუმჯობესება ADOS ტესტით შეფასების საფუძველზე - სოციალური ინტერაქციისა და კომუნიკაციის დადასტურებული არააუტისტური დიაპაზონი. თითოეული შემთხვევის შეფასების შედეგი განიხილებოდა მულტიდისციპლინარული გუნდური შეფასებით.

შედეგები

განვითარების და აუტიზმ-სპეციფიკური სკრინინგი ჩაუტარდა 2044 (სამიზნე პოპულაციის 77.1%) ბავშვს, ხოლო მათგან 17 (0.83%) იდენტიფიცირდა როგორც აუტიზმზე მაღალი რისკ-ჯგუფის ბავშვი. 17-ვეს ჩაუტარდა სრული დიაგნოსტიკური შეფასება. ნეიროგანვითარებითი დარღვევები გამოვლინდა საკვლევი ჯგუფის 3.07%-ში, ხოლო კონკრეტულად ასა - 0.88%-ში. ორი-ოთხი წლის ბავშვებში ასა-ს გავრცელება აღმოჩნდა 0.88%.

შემდეგ ეტაპზე, 44 აუტიზმის სპექტრის აშლილობის დიაგნოზის და ერთიდაიგივე ტიპისა და ინტენსივობის თერაპიის მქონე ბავშვზე მოხდა მონიტორინგი 36.2 თვის (SD - 2.5; min – 21; max - 36) განმავლობაში. ექვს (14%) შემთხვევაში სოციალური და კომუნიკაციური უნარები მნიშვნელოვნად გაუმჯობესდა, რაც დაადასტურა მულტიდისციპლინური ჯგუფის კლინიკურმა შეფასებამაც. ექვსივე შემთხვევა იდენტიფიცირდა როგორც ოპტიმალური გამოსავალი (OO) .

დასკვნა

ჩატარებული კვლევის შედეგად გამოვლინდა, რომ ორიდან ოთხ წლამდე ასაკში ნეიროგანვითარების დარღვევების გავრცელებაა 3,07%, ხოლო ასა-ს - 0,88%. ასა-ს შემთხვევათა 14%-ში შესაძლებელია ოპტიმალური გამოსავლის მიღწევა - სოციალურ-ემოციური განვითარების მნიშვნელოვანი გაუმჯობესება ფუნქციური უნარების შეზღუდვის გარეშე.

საკვანძო სიტყვები: აუტიზმის სპექტრის აშლილობა, გავრცელება/პრევალენტობა, ოპტიმალური გამოსავალი, პროგნოზი.

Abstract

Background

Autism spectrum disorder (ASD) is a complex neurodevelopmental condition characterized by impairments in social communication and social interaction in the presence of restricted, repetitive behaviors or interests with lifelong impacts. People with ASD might have poor prognosis however, according to some authors, individuals with diagnosed ASD can achieve typical functioning. Such phenomenon was described as an "optimal outcome" (OO).

Objective of the study

The objective of the study is to estimate the prevalence of ASD, identify its clinical characteristics and reveal possible predictors of OO of ASD.

Methods

The prospective cohort study was conducted in three steps: screening, diagnostic evaluation and re-evaluation. At the first stage of the study target population were 2651 children aged 2 to 4 years registered at the primary health care centers of Tbilisi. Screening underwent 77.1% of them (2044) with Ages and Stages Questionnaire (ASQ) and the Modified Checklist for Autism in Toddlers (M-CHAT).

At the second stage risk-group children were diagnostically assessed with: Autism Diagnostic Observation Schedule (ADOS), Autism Diagnostic Interview (ADI-R), and the Vineland Adaptive Behavior Scale (Vineland II). Final diagnosis was made by the multidisciplinary team.

At the third stage, 44 children diagnosed with ASD were received intervention of the same type and intensity - five applied behavioral therapy sessions (ABA) in a week. The dynamics of social and communication development were followed for 36 months. The optimal outcome (OO) was defined as the critical amelioration of ASD symptoms and improved functioning within the non-autistic range of social interaction and communication confirmed by the multidisciplinary team which were blinded for the baseline data.

Results

From 2044 (77.1% of total sample) screened children 17 (0.83%) were identified as risk-group for ASD, who underwent full diagnostic assessment. Neurodevelopment disorders were evident in 3.07% and ASD - in 0.88% of study group.

At the next stage 44 children with ASD receiving ABA intervention of the same intensity followed up about 36.2 months (SD 2.5; min – 21; max - 36). At the end of the study six (14%) children showed significant improvement in their social and communicative abilities to normal age range. Clinical assessment of multidisciplinary team confirmed that those cases were not met with diagnosis of ASD anymore. Those six cases further were considered as cases with OO.

Conclusions

The prevalence of neurodevelopmental disorders was 3,07%, and ASD – 0,88%. 14% of children significantly improved their social-emotional development up to no limitations of functional abilities.

Key Words: Autism Spectrum Disorders, Prevalence, Optimal Outcome, Predictors.

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List of Abbreviations

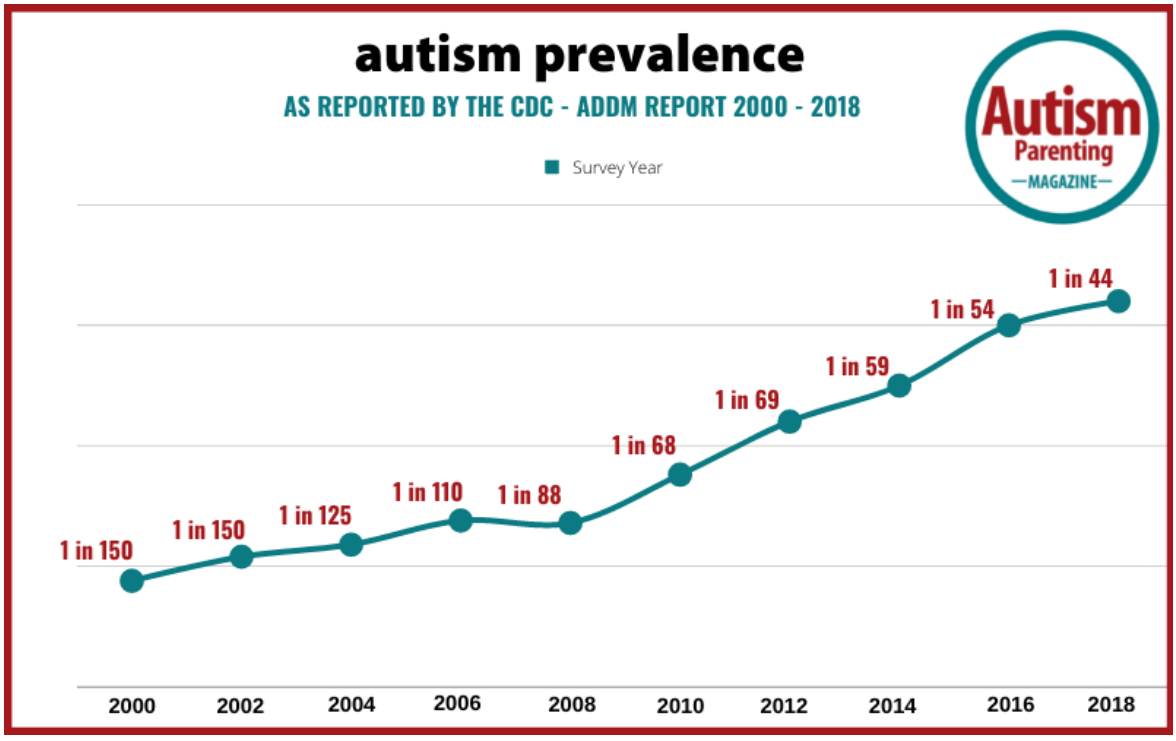
ASD	Autism Spectrum Disorder
OO	Optimal Outcome
ADOS	Autism Diagnostic Observation Schedule
M-CHAT-R	Modified Checklist for Autism in Toddlers-Revised
Vineland II	Adaptive Behavior Scales—Second Edition)
ASQ-3	The Ages and Stages Questionnaire, 3rd edition)
EIBI	Early and Intensive Behavioral Intervention)
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ICD-10	International Statistical Classification of Diseases
ABA	Applied behavior analysis
IQ	Intelligence Quotient
PIQ	Performance Intelligence Quotient
IQR	Interquartile Range
SD	Standard Deviation
min.	Minimum
max.	Maximum

Introduction

Research Topic

Autism and Autism spectrum disorders (ASD) are a diverse group of conditions, characterised by some degree of difficulty with social interaction and communication. Other characteristics are atypical patterns of activities and behaviours, such as difficulty with transition from one activity to another, a focus on details and unusual reactions to sensations (WHO., 2022). Epidemiological research show an increasing tendencies in the annual prevalence of ASD. Besides the true increase in the prevalence of ASD, there are different other reasons, such as a broader definition of ASD, changes in diagnostic criteria and screening tools, shifts in research methods, and increased awareness of ASD, have been suggested to contribute to this phenomenon (Durkin et al., 2017]. The prevalence is four times more in boys than girls [WHO, 2022]. The average prevalence of ASD in Asia, Europe and North America is estimated at 1% (Chiarotti et al., 2020, Fombonne, 2020). Graph #1 Illustrates the dynamics of changes in the prevalence of autism (Maenner., et al, 2021).

Graph 1. Dynamics of autism prevalence



The average prevalence of ASD in Asia, Europe and North America is estimated at 1% (Chiarotti et al., 2020, Fombonne, 2020). In the different findings by years, regarding international prevalence, the World Health Organization in 2018, estimated that 0.62% of the world's children had ASD. Other systematic reviews of prevalence studies internationally have produced similar summary estimates of approximately 0.7% (Baxter et al., 2015; Elsabbagh et al., 2012), though a review in China reported lower estimates (Wan, et al., 2013). The highest recent international prevalence estimate was 2.64% for 7- to 12-year-old children in South Korea in 2005–2009. This estimate was based on a two-stage screening-confirmation approach (Kim et al., 2011). National registries in Scandinavian countries provide a unique resource for estimating temporal trends. In 2011, ASD prevalence based on registry estimates exceeded 1% in Finland and Sweden and 1.5% in Denmark. These 2011 estimates reflect steady increases in age-specific ASD prevalence across birth year cohorts from 1990 to 2007 (Atladottir et al., 2015), mirroring reports in the United States (Christensen et al., 2016). In Sweden, much of the increase was attributed to improved documentation and identification of milder ASD (e.g., without accompanying intellectual disability) (Idring et al., 2015).

From the Autism and Developmental Disabilities Monitoring (ADDM) Network provided evidence that ASD prevalence per 1,000 children aged 8 years varied across the 11 ADDM Network sites, ranging from 16.5 (1.65%) in Missouri to 38.9 (3.89%) in California. The overall ASD prevalence estimate was one in 44 children aged 8 years. These estimates are higher than ADDM Network ASD prevalence estimates from previous surveillance years (Maenner.,et al, 2021).

The latest estimates of the prevalence of ASD worldwide, was published in 2021 by systematic review (Zeidan., et al, 2022). A median prevalence of 100/10,000 (range: 1.09/10,000 to 436.0/10,000). The median male-to-female ratio was 4.2. The median percentage of autism cases with co-occurring intellectual disability was 33.0%. Estimates varied, likely reflecting complex and dynamic interactions between patterns of community awareness, service capacity, help seeking, and sociodemographic factors.

Hypotheses linking factors that increase the likelihood of developing autism with variations in prevalence will require research with large, representative samples and comparable autism diagnostic criteria and case-finding methods in diverse world regions over time.

Reliable prevalence data from developing countries are still sparse, and despite growing interest over the past decade, formal study of the influence of global cultural variations on ASD awareness and diagnosis remains limited (Elsabbagh et al., 2012; Zaroff et al., 2012).

With ASD rates on steady increase, the scientists are more and more interested in uncovering the factors linked with this condition.

Although ASD is generally considered to be a chronic and lifelong condition, some studies show that there are a number of patients who achieve near-typical developmental parameters in their cognitive, adaptive, and social skills. The proportion of such cases may range from 3% to 25% (Helt et al., 2008). According to various data, high intelligence, good receptive language skills, verbal and motor imitation, and motor development are predictors of a good ASD outcome (Helt et al., 2008).

It is known that in children with autism, during early development, a reliable increase in head circumference is observed compared to the age- norm, although this parameter was not found to have a predictive value.

Most controlled studies report that good outcomes for ASD are associated with the use of behavioral intervention techniques. Tics, depression, and phobias are common later/residual symptoms even with good response to ASD (Helt et al., 2008).

Possible mechanisms for a good outcome may be: normalization of neuronal connections, which is facilitated by training or environmental factors, which contributes to more adequate realization of social stimuli, reduces stress and leads to general stabilization. Improvements in eating and sleeping habits have also been shown to be associated with better ASD outcomes (Helt et al., 2008).

ASDs are heterogeneous, multifactorial neurodevelopmental conditions. Currently, there is no effective treatment for ASD, but it is possible to manage the condition and improve the outcome. According to some studies, it is possible to significantly improve the level of functioning of individuals with ASD, almost approaching typical development.

Significance of the Study

Despite increasing interest in similarities and differences in the manifestations of the condition in different world regions, there is limited information about the incidence, cultural factors, diagnosis and management of ASD in low- and middle-income countries (LMIC), like Georgia.

The high socio-economic burden of the mentioned violation and the increasing indicators of its spread have led to the increasing attention of the scientific community towards ASD. Among them, in terms of the course of the disorder and the long-term outcome.

Studying the impact of pre-, peri- and postnatal risk factors on the development of ASD is becoming more and more relevant.

An accurate epidemiological description of ASD can help public health policy and planning for education, housing and financial support services, to address the current service provision gaps and may also inform service enhancement approaches in other LMICs.

Exploring the effect of pre-, peri- and postnatal risk factors on development of ASD will provide more insight not only into etiology of ASD and give possibility for early recognition and possible prevention of ASD.

In the case of ASD, the definition of the diagnostic output and the measurement methodology have changed significantly from time to time. From the 1960s to the 2000s, the definition of ASD outcome varied from "good" to "very poor" and relied on rather non-specific criteria (Rutter, Greenfeld, & Lockyer, 1967). It should be noted that these criteria were quite vague and imprecise, which created a significant problem for the validity of the studies and the mutual comparison of the results. Later, the Overall Outcome Rating (OOR) was developed - a scale based on independent living, social interaction/making friends, and self-actualization/employment opportunities (Patricia Howlin, Goode, Hutton, & Rutter, 2004). Subsequently, the mentioned scale was mostly used with certain variations, where different authors tried to take into account certain anthropometric or individual characteristics of the patient.

Such blurring of definitions and criteria was partly due to the "novelty" of autism as a medical nosology, where researchers tried to establish criteria for defining the course and

outcome of the condition. The gradation proposed by Rutter and colleagues was based on such definitions of autism outcome as: good, satisfactory (fair), poor and very poor outcome (Rutter et al., 1967). According to this criterion, a good outcome was defined as "an individual who leads a normal or near-normal lifestyle and is able to function at school or at work." A very poor solution was defined as "a person who cannot function independently". Obviously, there may be quite a large difference between different researchers in the evaluation of the "Typical or close to typical" condition, which creates a prerequisite for systematic bias and raises serious questions regarding the validity of the research results.

Since the 2000s, there have been trends toward developing more standardized, quantifiable criteria for autism diagnosis. These criteria are mainly based on empirical definitions of optimal social functioning, such as independent living, social relationships and competitiveness at work.

The first study that attempted to assign a numerical index of functioning to ASD output was that of Howlin and colleagues (P. Howlin, Mawhood, & Rutter, 2000). According to this study, ASD's outcome was assessed by the criteria of autistic behavior, language development/speech, establishing social relations and independence, where each criterion was presented with a score of 0 to 6 points. A score of 0 for each criterion reflected typical or near-typical functioning according to the same study, in 74% of cases, poor or very poor results of ASD were noted.

In most of the subsequent studies, the outcome of autism was presented on the Overall Outcome Rating (OOR) scale. It has three areas; It is represented by the total points of success at work, establishment of social relations and independent life. The total score finally gives us five categories, including: 0-2 points for very good, 3-4- good, 5-7- satisfactory, 8-10 poor and 11 were indicative of very poor outcome (Patricia Howlin et al., 2004). In the same study, after long-term follow-up, only 4% of individuals with ASD lived independently, and 57% had a poor or very poor outcome.

Relatively more optimistic data were obtained in another study, where a poor outcome was detected in 50%, and two individuals managed to work independently (Eaves & Ho, 2007).

In subsequent studies, which used the same or slightly modified evaluation criteria, approximately similar results were revealed, namely: in 61% of cases, a poor or very poor outcome was noted in one study, patients with an intelligence quotient (IQ) of 70 and above

had independent employment in almost half of the cases, which was significantly higher than similar rates in other studies (Farley et al., 2009). According to the results of this study, higher IQ was associated with a more optimistic prognosis of ASD.

According to some scientists, it is necessary to take into account the impact of environmental factors when assessing the field of ASD. In some cases, the support of the family or immediate surrounding society significantly changes the quality of personal and social needs and achievements. for example according to Halpern and his colleagues, it is important not only whether a person with ASD has reached developmental age-appropriate norms, but also whether a particular individual has reached the set goal and how these achievements are perceived by the individual and his immediate surrounding society (Halpern, 1993). To illustrate, we may consider such a case where the development indicators of a person with ASD meet the highest criteria in terms of job competitiveness and independent life, but at the same time does not have adequate support from the family, and does not like his work. According to the researcher, in such cases, it is premature to talk about the optimal outcome and the complete reverse development of ASD.

Over the past few decades, the diagnostic criteria for autism have changed considerably. This affected the representativeness of the conducted studies (Diagnostic and statistical manual of mental disorders, n.d.). In particular, earlier studies paid more attention to cases of classic autism, while in relatively recent studies, cases of mild autism and Asperger's syndrome are considered along with severe cases of autism. According to the data of recent studies, better results are obtained when evaluating the outcome of ASD. This is likely to depend on the activation of factors associated with a better outcome. For example: earlier referral of persons with ASD for qualified and complete rehabilitation, which is likely to lead to more optimistic outcome of the condition.

Some researchers are increasingly trying to define the concept of the relationship between the individual and the environment in determination of the outcome of ASD. Many studies indicate that low IQ and speech deficits are predictors of poor outcomes (Gillberg & Steffenburg, 2015). However, an individual with ASD who lives in a supportive environment and receives support from members of society may achieve a more optimistic level of outcome despite existing cognitive and verbal problems.

Purpose of the Study

The objective of the study is: 1) to estimate the prevalence of autism spectrum disorders (ASD) and identify its clinical characteristics and risk-factors in 2-4 years old Georgian children and 2) reveal possible predictors of OO in children with diagnosed ASD.

Research Questions

The main issues to be studied during the research will be:

- The prevalence of autism spectrum disorders in Georgia;
- The age of determining the final diagnosis;
- The age of admission to physician;
- The main reason for treatment;
- The age of parents and age difference between parents;
- Gender differences in the manifestation of the disorder;
- Correlation between prenatal, intranatal and postnatal factors and ASD;
- Impact of IQ score on outcome;
- Assessment of possible relationships of demographic, anthropometric, neurodevelopmental and environmental factors with the outcome of autism and identification of predictors;
- Assessment of sensitivity of the Georgian variant of the adapted screening-questionnaire (M-CHAT-R) and determining its potential for routine use.

Review of the Literature

Autism and Autism spectrum disorders (ASD) are a diverse group of conditions, characterised by some degree of difficulty with social interaction and communication. Other characteristics are atypical patterns of activities and behaviours, such as difficulty with transition from one activity to another, a focus on details and unusual reactions to sensations (WHO., 2022). ASD imposes a heavy economic burden on society and the patients' families (Gordon-Lipkin et al., 2018), as persons with ASD require considerable care, demanding significant financial resources. The direct and indirect costs of caring for children and adults with ASD in the United States in 2015 were estimated at $268.3 billion. Overall, the cost of education, health care, and other lifelong services for an autistic patient varies from $ 1.4 million to $ 2.4 million per year (Leigh et al., 2015).

Epidemiological research show an increasing tendencies in the annual prevalence of ASD. Besides the true increase in the prevalence of ASD, there are different other reasons, such as a broader definition of ASD, changes in diagnostic criteria and screening tools, shifts in research methods, and increased awareness of ASD, have been suggested to contribute to this phenomenon (Durkin et al., 2017]. The prevalence is four times more in boys than girls [CDC]. The average prevalence of ASD in Asia, Europe and North America is estimated at 1% (Chiarotti et al., 2020, Fombonne, 2020). In the different findings by years, regarding international prevalence, the World Health Organization in 2018, estimated that 0.62% of the world's children had ASD. Other systematic reviews of prevalence studies internationally have produced similar summary estimates of approximately 0.7% (Baxter et al., 2015; Elsabbagh et al., 2012), though a review in China reported lower estimates (Wan, et al., 2013). The highest recent international prevalence estimate was 2.64% for 7- to 12-year-old children in South Korea in 2005–2009. This estimate was based on a two-stage screening-confirmation approach (Kim et al., 2011). National registries in Scandinavian countries provide a unique resource for estimating temporal trends. In 2011, ASD prevalence based on registry estimates exceeded 1% in Finland and Sweden and 1.5% in Denmark. These 2011 estimates reflect steady increases in age-specific ASD prevalence across birth year cohorts from 1990 to 2007 (Atladottir et al., 2015), mirroring reports in the United States (Christensen et al., 2016). In Sweden, much of the increase was attributed to improved

documentation and, as seen in the CDC data, identification of milder ASD (e.g., without accompanying intellectual disability) (Idring et al., 2015).

From the Autism and Developmental Disabilities Monitoring (ADDM) Network provided evidence that ASD prevalence per 1,000 children aged 8 years varied across the 11 ADDM Network sites, ranging from 16.5 in Missouri to 38.9 in California. The overall ASD prevalence estimate was one in 44 children aged 8 years. These estimates are higher than ADDM Network ASD prevalence estimates from previous surveillance years (Maenner.,et al, 2021).

The latest estimates of the prevalence of ASD worldwide, was published in 2021 by systematic review. A median prevalence of 100/10,000 (range: 1.09/10,000 to 436.0/10,000). The median male-to-female ratio was 4.2. The median percentage of autism cases with co-occurring intellectual disability was 33.0%. Estimates varied, likely reflecting complex and dynamic interactions between patterns of community awareness, service capacity, help seeking, and sociodemographic factors.

Hypotheses linking factors that increase the likelihood of developing autism with variations in prevalence will require research with large, representative samples and comparable autism diagnostic criteria and case-finding methods in diverse world regions over time. Reliable prevalence data from developing countries are still sparse, and despite growing interest over the past decade, formal study of the influence of global cultural variations on ASD awareness and diagnosis remains limited (Elsabbagh et al., 2012; Zaroff et al., 2012).

With ASD rates on steady increase, the scientists are more and more interested in uncovering the factors linked with this condition.

Although ASD is generally considered to be a chronic and lifelong condition, some studies show that there are a number of patients who achieve near-typical developmental parameters in their cognitive, adaptive, and social skills. The proportion of such cases may range from 3% to 25% (Helt et al., 2008). According to various data, high intelligence, good receptive language skills, verbal and motor imitation, and motor development are predictors of a good ASD outcome (Helt et al., 2008). However, in this research the overall severity of ASD symptoms was not associated with diagnostic outcome. In addition to the above, earlier age at diagnosis and diagnosis of pervasive developmental disorder unspecified (ICD–10; F84.9) were also associated with a favorable outcome. In contrast, the coexistence of

epileptic seizures, intellectual impairment, and genetic syndromes were predictors of poor outcome. It is known that in children with autism, during early development, a reliable increase in head circumference is observed compared to the age- norm, although this parameter was not found to have a predictive value. Most controlled studies report that good outcomes for ASD are associated with the use of behavioral intervention techniques. Tics, depression, and phobias are common later/residual symptoms even with good response to ASD (Helt et al., 2008).

Possible mechanisms for a good outcome may be: normalization of neuronal connections, which is facilitated by training or environmental factors, which contributes to more adequate realization of social stimuli, reduces stress and leads to general stabilization. Improvements in eating and sleeping habits have also been shown to be associated with better ASD outcomes (Helt et al., 2008).

ASDs are heterogeneous, multifactorial neurodevelopmental conditions. Currently, there is no effective treatment for ASD, but it is possible to manage the condition and improve the outcome. According to some studies, it is possible to significantly improve the level of functioning of individuals with ASD, almost approaching typical development.

To our knowledge, the prevalence of ASD has not been estimated in Georgia or other post-Soviet countries though such information is fundamental to the provision of adequate medical and educational resources for these children.

Establishing prevalence of ASD in Georgia will help in change policies for persons with ASD, including planning of needed services and professionals to fulfill requirement of all persons with ASD.

Epidemiologic investigation of potentially modifiable risk factors will catalyze further advances in research and public health; improve understanding of the etiology and pathophysiology of ASD as well as pharmacologic and psychosocial interventions for ASD.

I. Etiology of autism

ASD has no single known cause. Many etiological factors can play a role, however, the influence of hereditary factors and certain environmental conditions can still be seen in this background. Genetic etiology of ASD is widely recognized. Among the many possible genetic factors, approximately 5–10% are associated with known chromosomal abnormalities, including maternally inherited 15q11–q13 or de novo mutational variants that determine synapse function (Lichtenstein, et al, 2010). Genetic risk factors for ASD overlap with other diverse developmental and psychiatric disorders (Wu Y et al.,2020; Willsey HR et al; 2021). A variety of genetic and environmental factors have been associated with ASD, but none are absolutely specific for the development of ASD (Hirota, King 2023).

Some studies suggest that maternal viral infections (e.g., rubella), prenatal exposure to valproic acid, or thalidomide may be etiological factors for autism (Montigny, et al, 2017). A meta-analysis of studies identified that maternal factors, such as gestational hypertension (odds ratio, 1.4 [95% CI, 1.2-1.5]), overweight before or during pregnancy (relative risk [RR], 1.3 [95% CI, 1.2-1.4]), preeclampsia (RR, 1.3 [95% CI, 1.2-1.5]), and maternal age of 35 years or older (RR, 1.3 [95% CI, 1.2-1.5]) were associated with higher rates of ASD in offspring (absolute rates not provided) (Kim JY., et al; 2019). In addition, cohort and case-control studies reported that advanced paternal age can be the contributor - 21% increase in ASD diagnosis in offspring for every 10-year increase in paternal age (Wu, et al; 2017), medication use in pregnancy, and both short (<12 months) and long (≥72 months) periods between pregnancies (Zerbo, et al.2015) were associated with an increased risk for the diagnosis of ASD in offspring. In addition to the above, studies indicate that individuals with autism are more likely to present with suboptimal levels of pre-perinatal and postnatal health, including low Apgar scores and neonatal distress. Contrary to this, despite the large differences of opinion among the population, there is no research/scientific evidence regarding the ASD and measles-rubella-mumps vaccines (the effects of the vaccine stabilizer - thimerosal) (Taylor, et al, 2014).

One of the pronounced anthropometric characteristics in ASD is macrocephaly, which is mainly manifested at 12-24 months. Structural neuroimaging reveals abnormal growth of the cortex and white matter, especially in the frontal and temporal lobes, as well as in the

amygdala region. Magnetic resonance tractography (Diffusion tensor imaging) reveals the disconnection of white matter fibers between functionally important areas of the brain. Functional magnetic resonance imaging studies also demonstrate reduced cortical connections in the brain, leading to impaired speech, working memory, social perception, and problem-solving functions (Vissers, et, al, 2012).

II. Optimal Outcome and ASD

2.1 ASD Developmental Trajectory and Possible Outcome

When describing the outcome of the disorder in patients with ASD, a large number of cognitive, linguistic, social and behavioral functioning characteristics are used, which ultimately creates a certain problem in terms of mutual comparison of different studies. Most patients experience difficulties associated with autism spectrum disorders in speech, cognitive, and behavioral characteristics during adulthood (Billstedt, et al, 2005; Cederlund, et al, 2008; Howlin, et al., 2004; Seltzer et al., 2003; Sigman & McGovern, 2005). Individuals diagnosed with ASD often experience significant deficits in key areas such as employment, interpersonal relationships, and independent living during adulthood (Eaves & Ho, 2007; Howlin, et al, 2013).

Although for years, ASD was perceived as a condition that usually had a high probability of a poor outcome, in the last decade it has been reported that there are individuals with ASD who are making significant progress in their individual development. In contrast to other neurodevelopmental disorders, where the course and prognosis of the disease are practically predetermined and static, in the case of ASD there is noticeable variability in the course of the disorder and the heterogeneity of the expression of symptoms in the case of a some individual (here we can use the well-known expression: "when you meet one person with autism, you've met one person with autism", (Dr Stephen Shore). Lord and colleagues (Lord et al., 2012) described significant changes in intellectual functioning, social communication, and stereotypic behavior in a study group of 85 individuals diagnosed with ASD in early childhood and followed up periodically until age 17. According to their data, it was revealed that an IQ of 70 and above by the age of about 9 years was associated with a very good outcome of the diagnosis. This group significantly exceeded the rest of the individuals participating in the study in terms of indicators of cognitive, speech, stereotypic sensory and motor behavioral patterns. According to the authors, this phenomenon may have a certain biological and genetic basis, which is the subject of further study.

Another study, where the data of about 6000 children with ASD between the ages of 2 and 14 were evaluated, found several patterns that distinguished these patients from each other

according to the trajectory of the disorder course. It was high-functioning, medium-high, medium, medium-low, low and so-called. Those individuals that the authors called the Bloomers Group (Fountain, Winter, & Bearman, 2012). It was in this group that there were cases where, despite the seriousness of the condition at the time of diagnosis, they reached the level of practically satisfied development and functioning by the age of 10 years. A special dynamic of development in these individuals was revealed around the age of 6 years. It should be noted that the high intelligence of the mother and the high socio-economic status of the family were more represented in this category of individuals.

2.2 Factors Contributing to a Positive Outcome

According to various research data, the predictors of a good outcome of ASD are: high cognitive abilities or the absence of intellectual disability; high level of functioning prior to diagnosis, particularly in terms of verbal and non-verbal communication skills; diagnosis of Asperger's syndrome, or pervasive disorder - unspecified (both were removed from the diagnostic classification of DSM-V) and early intervention.

High intellectual abilities or the absence of mental retardation can be confirmed as predictors of a positive outcome for ASD. It should also be noted that high intelligence does not guarantee a positive outcome for ASD. Studies indicate that high intelligence is an important, but not the only factor for a positive outcome of ASD (Billstedt et al., 2005; Fein et al., 1999; Mukaddes, et al, 2014; Sallows & Graupner, 2005; Stevens et al., 2000; Turner & Stone, 2007).

IQ 70 and above is uniquely related to a positive outcome of autism in terms of social relations, especially independent life and employment, although it should be noted that the course of the disorder in persons with good intellectual abilities is characterized by considerable variability. According to the authors, IQ appears to be an important predictor, however, only in combination with certain contributing environmental factors (Anderson, et al, 2014; Howlin, et al, 2014).

A high level of adaptive functioning was also significantly associated with a positive ASD outcome. It was observed by a group of researchers that in individuals who no longer had symptoms of ASD by the age of 19, significant improvements in social and communication

skills were revealed by the age of 2-3 years (Eaves & Ho, 2007; Howlin et al., 2013; Smith, Groen, & Wynn, 2000; Stevens et al., 2000). Another study also found that imitation ability, before the intervention, high IQ level, better receptive language, level of social interaction, and adaptive skills were associated with a more favorable outcome in ASD. Another group of authors also concluded that higher levels of functioning and less severe ASD symptoms at 2 years of age were statistically significantly associated with a positive diagnostic outcome regardless of the type of intervention (Anderson et al., 2014; Darrou et al., 2010; Eaves & Ho, 2004).

Less severity of the disorder, as manifested by a diagnosis of Asperger's syndrome and pervasive disorder - unspecified, is associated with a better outcome of ASD, although the data in this regard are mixed. Some studies have linked the severity of the condition to a positive outcome, but other studies have not confirmed this. Moreover, the outcome is highly variable despite early and intensive treatment measures (Cederlund et al., 2008; Lord et al., 2012; Sutera et al., 2007).

Another factor that most studies have found to be associated with positive outcomes is early and comprehensive intervention (Granpeesheh, et al, 2009; Turner, et al, 2006). Most researchers believe that early brain plasticity leads to significant improvement in ASD symptoms in children who undergo early intensive rehabilitation (Cicchetti & Curtis, 2015). Neuroplasticity is the ability of the brain to undergo dramatic and sustained changes in response to exposure to positive environmental factors. Considering the above, they try to diagnose ASD as early as possible in order to ensure early intensive intervention.

The impact of early behavioral intervention models on ASD management and outcomes has been documented in numerous studies. Early comprehensive treatment aims to address behavioral problems and improve language skills as well as social behavior. This is especially effective when intervention is carried out from early childhood, usually between 2 and 8 years of age. The early rehabilitation model proposed by Lovaas (Lovaas, 1987) is described as Early Intensive Behavioral Intervention (EIBI), which in turn is based on the principles of Applied Behavior Analysis (ABA) (Reichow, 2012; Reichow & Wolery, 2009; Virués-Ortega, 2010). This method is designed to work face-to-face with the child, guided by a qualified therapist in a structured environment and of sufficient duration. According to Lovaas' data, 47% of patients who received intensive behavioral therapy showed a significant

improvement of autism symptoms compared to a control group, where minimal rehabilitative intervention was implemented, and where similar resolution was observed in only 2% of individuals.

According to the same study, relief from the symptoms of ASD implies intellectual and educational functioning within the range of normal indicators. As a result of a long-term observation of the same children, significant reduction of autism symptoms was noticed and improvement continued even in adulthood – independence in activities of daily living skills. Long-term follow-up of patients with ASD has consistently demonstrated that individuals receiving EIBI services often revealed significant improvement of speech and language, and adaptive behavior (McEachin, Smith, & Lovaas, 1993).

The percentages of the optimal outcome for autism are quite variable according to different studies, which is due to the differences in the definition of the best outcome between the studies, as well as the different starting conditions of the study group at the beginning of the study (IQ, severity of symptoms, etc.). For example, a study by Cohen and colleagues found that individuals assigned to an early intensive behavioral intervention group had significantly higher IQ and adaptive skills compared to a control group. 29% of the early intervention group engaged in the regular learning process without additional help, while a similar result was noted in only 5% of the control group.

2.3 Optimal Outcome in Individuals with ASD

According to various estimates, from 3 to 25% of children with ASD, over time almost significantly "lose" the symptoms characteristic of autism (Helt et al., 2008). Other studies have reported even higher optimal outcome (OO) rates, particularly in individuals where EIBI therapy was used. According to different authors, the optimal solution was found in 47% and 48% of EIBI therapy, respectively (Lovaas, 1987). When evaluating these data, a very important question arises, how reliable and scrupulous is the determination of the optimal solution and hence the indicators, which are given in different studies. Studies have used more or less different definitions of OO for both baseline diagnosis and outcome (Sallows & Graupner, 2005; Turner & Stone, 2007). There are a variety of possible long-term outcomes associated with child and adolescent mental health and neurodevelopmental

conditions. Costello and Maughan (2015) suggest that the term 'optimal outcome' captures the absence of current symptoms, co-occurring conditions, and functional impairment (Costello & Maughan, 2015). In ASD group, there exists a group of individuals who met criteria for ASD in childhood who no longer meet criteria later in development. A myriad of terms has been used to describe this group: optimal outcome (Fein et al., 2013; Mukaddes, et al, 2014); optimal progress (Moulton, et al, 2016); bloomers (Fountain, et al, 2012); best possible outcome (Costello & Maughan, 2015); very positive outcome (Anderson, et al, 2014); and recovery (Mukaddes et al., 2014). At the same time, it should be noted that the data of prospective longitudinal studies in terms of the study of OO are quite scarce, which puts a certain doubt on the external validity of the data on OO and is a problem in terms of mutual comparison of research data.

2.4 Conceptual and Methodological limitations of Autism Optimal Outcome Studies

At this stage, there is still no established standard definition of what OO means. When evaluating OO, researchers have used different criteria for how OO or complete reversal of the symptoms of the disorder is defined. The oldest research in this regard defines the criteria of OO as a normal range IQ and full involvement in the learning process (Mundy, Sullivan, & Mastergeorge, 2009). In this regard, some questions arise regarding the validity of the given criteria, especially in terms of IQ, because an individual with ASD can freely have normal IQ values (67%) and also participate in the educational process without external assistance. Later studies revealed that cases with OO defined by this criterion initially presented with less severe forms of ASD, such as by diagnosis - Asperger's syndrome or pervasive disorder, unspecified. Most of these patients had relatively better IQ, and speech and language scores at baseline (Helt et al., 2008). Another important problem, which prevents the synthesis of the results of different studies, is the absence of objective criteria for the diagnosis of ASD. Prior to the publication of the Autism Diagnostic Observation Schedule (ADOS 2001), the diagnosis of ASD was based on individual clinician judgment and parent input (Lord & Rutter, 2012).

2.5 Rates of Functional Improvement in Children with Optimal Outcome

The gold standard for the diagnosis of ASD is a professional-approved diagnosis of ASD before the age of 5 years with accompanying speech delay (no speech by 18 months and no phrasal speech by 24 months) (Fein et al., 2013; A. J. Orinstein et al., 2015). ; A. Orinstein et al., 2015; Suh et al., 2014). The OO criteria proposed by this group of researchers are: a) falling within 1.5 standard deviations of standard verbal, non-verbal, full-scale IQ scores; b) ADOS scores - in below the cutoff and typical relationships with peers; c) Vineland's communication and socialization scores within 1.5 standard deviation; and d) no need of assistance for learning at school.

OO criteria according to other studies also indicate functional independence within the range of typical development. For example, researchers identified a group of children with ASD who achieved age-range levels of cognitive, speech, adaptive, academic, and social functioning in response to early behavioral therapy. According to Sutera, the criteria for OO in children diagnosed with ASD are typical development of adaptive and cognitive skills, as well as the absence of unspecified criteria for autism or pervasive disorder diagnosis (Sallows & Graupner, 2005; Sutera et al., 2007). Children with OO had speech and language development (Suh et al., 2014; Tyson et al., 2014), academic performance (Troyb, Orinstein, et al., 2014), executive functioning (Troyb, Rosenthal, et al., 2014), and adaptive behavior (Kelley, Naigles, & Fein, 2010) as typically developing peers.

2.6 Residual Symptoms Associated with the Optimal Outcome

According to various research data, individuals who have achieved OO continue to have attention deficit. According to Kelly, children with OO had borderline attention deficit disorder (Kelley, Paul, Fein, & Naigles, 2006). According to the data of another study, children with OO showed characteristic signs of attention deficit and hyperactivity syndrome more frequently than their peers with typical development (A. Orinstein et al., 2015). Notably, attention deficit and impulsivity were also seen in children who retained a

diagnosis of high-functioning ASD. Children who have reached OO may still have difficulties with language and speech development. According to one study, although the grammatical errors during speaking of 5-9-year-old children with OO were still evident compare to peers with typical development, also, difficulties in the development of the pragmatic and semantic domains of language (Kelley et al., 2010). However, observation of the same individuals revealed that between the ages of 8 and 14, language problems regressed (A. J. Orinstein et al., 2015; Suh et al., 2014; Tyson et al., 2014). In other studies, children with OO did not show semantic or pragmatic language problems, but idiosyncratic speech and self-correction deficits was evident compared to typically developing peers (Suh et al., 2014).

Collecting more and more evidence on the OO, researchers concluded that persons who no longer meet criteria for an ASD is not necessarily inherent in a good outcome and it may not reflect the identity and values of every autistic individual. Autistic self-advocacy (e.g., the *Autistic Self Advocacy Network*), neurodiversity, and intersectionality perspectives point to the need for reframing outcomes in ASD (e.g., Georgiades & Kasari, 2018). McCauley and colleagues (2020) suggested criteria for good outcomes of ASD, that include autonomy, daily living skills, and relationships and employment/activities outside the home.

2.7 Functioning of Adults with Optimal Outcomes

The optimal outcome has become relevant in the last few decades. Because of this, there are quite few studies conducted with a prospective, longitudinal observation design, which would allow us to observe patients with OO for a long time. The first prospective study was conducted by Anderson and colleagues in 2014 and examined the level of functioning in adulthood in patients with optimal ASD output. By age 19, individuals with OO had significantly higher verbal IQ (111 points) and higher levels of adaptive functioning (mean Vinland composite score = 101) compared to individuals who still had symptoms of autism. In addition, those with OO had significantly lower levels of stereotypic behaviors, social deficits, irritability, attention deficit disorder, and depression, while having average or above average academic achievements. In addition, persons with OO were four times more likely to live independently compared to individuals diagnosed with ASD. According to the

authors, it is very important to conduct a long-term, prospective observational study of patients with ASD, which will allow us to observe the development of ASD and the dynamics of patients' functioning with different outcomes (Anderson et al., 2014). In recent study of Deborah Fein who is the pioneer in OO, examining long-term outcomes of individuals experiencing LAD, she gathered the data on the domains suggested by Costello and Maughan (2015). Faced with the demands and stresses of the transition into adulthood, ASD characteristics such as difficulty with social interaction and perseverative interests might reemerge. Also, appearance of conditions known to co-occur with ASD (especially anxiety and depression), functional impairment, as measured by adaptive functioning in the areas of friendships and romantic relationships, engagement in current school or employment, and autonomy (living arrangements, self-care, and financial independence) is the most challenging fields to be observed to. This approach aligns with the view that LAD status is not sufficient for understanding outcomes in ASD (e.g., Georgiades & Kasari, 2018).

III. Influence of Enviromental, family and other factors on the course of ASD

3.1 Environmental Factors and Their Influence On the Course of ASD toward OO

Many studies have focused on the course of ASD when early intensive intervention was used. According to one study, individuals who reported OO were more likely to be involved in intensive treatment services (Kelley et al., 2010). A retrospective study also confirmed that in persons with OO, there were a higher parental awareness about autism symptoms, which led to early referral to a specialized center and, therefore, led to early intensive rehabilitation (A. J. Orinstein et al., 2014). In addition, children with OO were found to use EIBI therapy more frequently compared to individuals who still had symptoms of ASD. Along with this, the frequency of psychiatric medication use was higher among individuals with still having ASD, which the authors believe may be due to higher rates of behavioral problems and depressed mood (Orinstein et al., 2014).

Research by Anderson and colleagues also highlighted that early intervention is associated with better outcomes for autism (Anderson et al., 2014). However, it is difficult to draw conclusions about cause and effect from this study, namely whether early intervention really leads to OO, or whether early intervention itself is due to other contributing factors such as parental education, awareness level, family income, etc. which at the same time is the determinant of the optimal outcome. According to some studies, sociodemographic characteristics are associated with the outcome of ASD (Eaves & Ho, 2004; Fountain et al., 2012). However, the mechanism by which socioeconomic factors influence the outcome of ASD is not clear. It is likely that, due to financial security, it leads to the possibility of early intensive intervention. In addition, parents' high awareness and involvement in the rehabilitation process may play a role and lead to a better outcome in patients with ASD.

3.2 Influence of Family and Parenting Style on the Course of ASD

Sufficient data have been accumulated to illustrate that inadequate support and inadequate response from the family to a child with ASD can lead to developmental delay and slow progress. The study on the influence of family and parents on the course of ASD was taboo for some period. The main reason was existing invalid etiological factor of "refrigerator mothers", which received serious criticism and was not accepted by the scientific community (Bettelheim, 1967). The anecdotal evidence led to a decrease in the scientific community's interest in researching the influence and importance of family and parenting on the course of ASD. Nevertheless, recent studies clearly indicate that the attitude, support, and position of the family, especially the mother, towards the child with ASD is critically essential in post-diagnostic development.

Various empirical studies based on the principles of EIBI therapy have highlighted the central role of parental involvement in the outcome of ASD. Moreover, the involvement of parents as co-therapists and team members was found to be very important in improving the outcome. Dawson and colleagues concluded as a result of research that the active involvement of parents in the therapy process (parent-mediated therapy, which became the basis of early intervention) may lead to the acceleration of the development of functional connections of the brain and the improvement of neurodevelopmental outcome (Geraldine Dawson, 2008; Koegel, Koegel, Harrower, & Carter, 1999).

A specific index of parenting behavior has been found to be associated with child outcome with ASD (Siller & Sigman, 2002). Studies have shown that the mother's relationship style with a child with ASD is related to certain regulatory processes, which ultimately leads to better indicators of children's adaptive and self-regulatory skills, as well as control of negative emotions (Gulsrud, et al, 2010; Hirschler-Guttenberg, et al, 2015). There is an opinion that the influence of the parental factor is much more pronounced in children with ASD compared to their peers with typical development. The existing evidence of the impact of parental factors provides a basis for future research to examine parental sensitivity, ASD problem-solving, parental psychopathology, and characteristics of the relationship with a child with ASD (Oppenheim, et al, 2012; Siller & Sigman, 2002).

3.3 Child development - Language and Cognitive Development as Factor for Optimal Outcome

In addition to environmental factors, a child's language skills and cognitive characteristics also play an important role in the outcome of ASD. Early language skills are one of the important characteristics associated with better outcomes of ASD (Eaves & Ho, 2004; Howlin, et al, 2009; Stevens et al., 2000; Sutera et al., 2007). Some studies confirm that language development and skill to follow verbal instructions, were a predictor of OO, although at the same time, prospective studies did not reveal a similar association between verbal or non-verbal skills and OO (Pellicano, 2012; Sutera et al., 2007). According to the same study, in 19% of cases, symptoms of ASD were no longer observed according to ADOS criteria. One factor that this study found to be associated with OO is the age when intensive intervention was started. In addition, the absence of intellectual disability was also a predictor of a positive ASD outcome. However, research by Sutera and colleagues found that some persons with OO did not have IQs in the average range. There is a growing view that there may be some unique intellectual capacities whose activation and use, under the conditions of favorable environmental factors, may lead to the adequate functioning of an individual with ASD despite having an IQ below average (Billstedt et al., 2005; Sigman & McGovern, 2005; Stevens et al., 2000; Turner & Stone, 2007).

According to some research data, relatively better development of visuospatial skills is one of the characteristic strengths of patients with ASD. Modern functional neuroimaging methods have shown the existence of a different, unusual pattern of visuospatial perception compared to peers with typical development (Baron-Cohen & Belmonte, 2005; Koldewyn, Jiang, Weigelt, & Kanwisher, 2013; Muth, Hönekopp, & Falter, 2014). However, in specific cases, neuroimaging methods could not identify specific patterns of strong skills, and in this sense, the data are contradictory. While studies have identified unique cognitive abilities in individuals with ASD, significant variability in these abilities is striking (Patricia Howlin et al., 2009). Based on the interaction of genetic and environmental factors, the phenotype of a specific individual signs of ASD is formed. Researchers are trying to find out how this interaction affects the neurocognitive development of ASD, especially in cases where individuals from the same family or micro society who have almost identical developmental

conditions show very different patterns of the course of the disorder (Baron-Cohen & Belmonte, 2005). In this direction, more targeted studies are needed to study the dependence of language and cognitive abilities on environmental factors and genetic predisposition.

Recently considerable progress achieved in increasing autism awareness and public health response worldwide and in Georgia. In many cities of Georgia municipal programs provide 20 hour/month sessions to children with ASD. Despite the progress there is no epidemiological studies offering objective indicators of the impact of autism, including estimates of cases and their associated social and economic impacts.

Despite the fact that 95% of all <5 years of age with developmental disabilities including ASD live in low- and middle-income countries, the vast majority of ASD research studies to date have been conducted in high-income countries, resulting in a research gap in studies from low-and middle income (LAMI) countries (Durkin et all, 2015; Lord, et al, 2020) like Republic of Georgia.

Methodology

I. Description of the instruments used in the study

The study design was prospective cohort and conducted in three steps: screening, diagnostic evaluation and re-evaluation after min 3 years.

Inclusion Criteria followed the staged approach and were as such:

- For the first stage:
    - Age of children (2-4 years)
    - Registration address (Vake, Saburtalo and Dighomi, Tbilisi city)
    - Obtained informed consent from the parent or other responsible person
- For the second stage:
    - Risk-group children revealed after screening stage
    - Obtained informed consent from the parent or other responsible person
- For the third stage:
    - Children diagnosed with: childhood autism, atypical autism or pervasive developmental disorder, unspecified.

All children with significant neurological or somatic co-morbidity revealed at any stage, which would make it impossible to observe the patient, were excluded from the study.

At the first stage of the study (from January 2009- to February 2010) target population were children aged 2 to 4 years (born between January 1, 2006 and December 31, 2008) who were registered at the primary health care centers of three districts of Tbilisi: Vake, Saburtalo and Dighomi (2651 children). Screening underwent 2044 children (77.1% of total sample). Out of 2044 screened children, 1019 (49.85%) were boys and 1025 (50.14%) were girls.

For the screening of children's development **Ages and Stages Questionnaire** (ASQ) was used, which shows strong evidence of validity and reliability and is recommended by the American Academy of Pediatrics for detection of developmental delay in infants and young children. In low- and middle-income countries it is especially important to use a simple screening tool, which is scientifically reliable and valid, culturally appropriate, brief, user-friendly, and easy to learn and administer (Zirakashvili, et all, 2018).

The ASQ is a set of 20 age-specific questionnaires intended for use from the age of 1 month to 5 1/2 years. Each questionnaire consists of 30 items, covering five domains:

Communication, Gross Motor, Fine Motor, Problem Solving, and Personal Social. Each domain has six scored items. Scoring rules and final decision-making procedures are well described elsewhere.

Recent literature suggests that the ASQ is an appropriate screening tool for different cultures. Several studies have examined the psychometric properties of the ASQ in cultures outside the United States (e.g., Australia, Brazil, Canada, Chile, China, India, Netherlands, Norway, Peru and Portugal). The ASQ-3 is validated and standardized for young children living in Georgia (Zirakashvili et al., 2018).

The ASQ was translated and culturally adapted. Mean scores per domain were compared to US normative scores. Multivariate analysis was performed to detect variables independently associated with ASQ cutoff scores. The ASQ after cultural adaptation was easily administered to all age groups. Cronbach's alpha values for all age groups varied from 0.643 to 0.824 across areas. Significant differences were found in cutoff points between those of the Georgian ASQ and the original US reference population in most domains across age groups. Analysis revealed that gender of children was associated with Communication (B, 0.453; p=0.01), Fine motor (B, 0.457; p=0.01) and Personal - social (B, 0.576; p=0.001) areas showing that scores of girls are more frequently distributed above cutoff points. The Georgian version of ASQ seems to be an adequate measure for screening of child development. The study was published in Journal of Child and Family Studies, 27(3), 739-749, 2018.

All family doctors were asked to complete the ASQ with help of parents of children registered their work area. Children whose scores were below the cutoff (56 children) for more than two domains were considered as a risk group. The most frequent were cases with scores below the cutoff in one domain - 6.57%. 3.06% of children had problems in two, 0.88% - in three and 0.55% - in four domains. Only 0.05% of children's scores were below the cutoff in all five domains.

Additionally, family doctors with help of parents screened all children with the **Modified Checklist for Autism in Toddlers** (M-CHAT). Three or more abnormal answers have had 17 children (0.08%).

This screener is autism-specific measure, which is commonly used in many countries. The CHAT, developed in the United Kingdom, was the first autism-specific screening measure.

Robins et al adapted it for use in the United States in 2001, producing the M-CHAT (Robins, et al, 2001). The screener composed of 23 yes or no items. A child is considered as screen positive at the initial screening if he or she has abnormal answers for 2 of the 6 critical items or 3 of any 23 items. If the child screens positive, it does not constitute a diagnosis but indicates significant risk of autism, suggesting the need for evaluation with a gold standard test to diagnose autism. The M-CHAT was originally validated for children between 16 and 30 months of age, but many studies have used an upper age limit of 36 months or more (Canal-Bedia et al., 2011; Snow and Lecavalier, 2008).

At the second stage of the study (From May 2010-to November 2010) all children of the risk group were evaluated by a multidisciplinary team and all of them assessed with an autism diagnostic tests Autism Diagnostic Observation Schedule (ADOS), as well as a test to assess adaptive behavior – Vineland Adaptive Behavior Scales (Vineland II).

The Autism Diagnostic Observation Schedule (ADOS) is one of the few standardized diagnostic measures that involves scoring direct observations of the child's interactions and that accounts for the developmental level and age of the child. The ADOS is recommended in several Best Practice Guidelines as an appropriate standardized diagnostic observation tool (California Department of Developmental Services, 2002; Filipek et al., 1999, 2000; National Research Council, 2001). It includes a standardized administration of interactive activities introduced by the examiner, designed to elicit social interactions, communication and repetitive behaviors for the purpose of diagnosing an ASD (Lord et al., 2000; Lord, Rutter, DiLavore, & Risi, 2001). The measure takes 30 to 60 minutes to administer and consists of four different modules for use with individuals of different developmental and language levels. Activities vary based on the language level and chronological age of the child. For example, Modules 1 and 2, which are designed for use with children with a language level of less than 48 months. Modules 3 and 4, which are designed for older children, adolescents, and adults who have the ability to use complex sentences and talk about things that are not immediately present, include questions about emotions and relationships as well as retelling a story from a book and demonstrating a routine activity. The ADOS is standardized in terms of the materials used, the activities presented, the examiner's introduction of activities, the hierarchical sequence of social presses provided by the examiner, and the way behaviors are coded or scored. Following the administration of the ADOS, behaviors are coded using a 0-

to 3-point coding system, with a 0 indicating that the behavior is not abnormal in the way specified in the coding description and a 3 indicating that a behavior is abnormal and interferes in some way with the child's functioning.

ADOS classifications are based on specific coded behaviors that are included in a scoring algorithm using the DSM-IV diagnostic criteria, resulting in a Communication score, a Reciprocal Social Interaction score, and a Total score (a sum of the Communication and Reciprocal Social Interactions scores). Scores are compared with an algorithm cut-off score for Autism or the more broadly defined ASD in each of these areas. If the child's score meets or exceeds cut-offs in all three areas, they are considered to meet criteria for that classification on the measure. The authors reported good inter-rater reliability estimates on the Communication, Reciprocal Social Interaction, Total, and Stereotyped Behaviors and Restricted Interests domains, with intraclass correlations ranging from 0.82 to 0.93 (Lord et al., 2001). Test-retest reliability was also good, with intraclass correlations ranging from 0.73 to 0.82 on the Communication and Reciprocal Social Interaction domains, and 0.59 to 0.86 on the Stereotyped Behaviors and Restricted Interests domain. Published validity studies also suggest good predictive validity, with sensitivities ranging from 90% to 97%, and specificities ranging from 87% to 94% for autism/ASD versus other clinical diagnoses (Lord et al., 2001). Since the ADOS became commercially available through Western Psychological Services (WPS) in 2001, it has become more familiar to practitioners and purchased widely for use within school and community settings. The authors of the ADOS indicate that it should be used by experienced clinicians who have received appropriate training (Lord et al., 2001).

The Vineland Adaptive Behavior Scales, Second Edition (Vineland-II) is the leading instrument for supporting the diagnosis of intellectual and developmental disabilities. Since the beginning, Vineland Adaptive Behavior Scales has been a leading measure of personal and social skills needed for everyday living. All Vineland-II forms aid in diagnosing and classifying intellectual and developmental disabilities and other disorders, such as autism, Asperger Syndrome, and developmental delays. The Vineland II now includes different forms: Survey Interview, Parent/Caregiver Rating, Teacher Rating, Expanded Interview. These scales are organized within a three-domain structure: Communication, Daily Living, and Socialization. This structure corresponds to the three broad domains of adaptive

functioning by the American Association of Intellectual and Developmental Disabilities: Conceptual, Practical, and Social. In addition, Vineland-II offers a Motor Skills Domain and an optional Maladaptive Behavior Index to provide more in-depth information about clients. Vineland II is updated with new norms, expanded age range, and improved items. It is useful for diagnosis, qualification for special programs, progress reporting, program and treatment planning, and research, and offers both respected semi-structured interview format which focuses discussion and gathers in-depth information, and also offers convenient rating forms. Each child diagnostic observation process was video-recorded. The final diagnoses were made via the clinical judgment of the experienced multidisciplinary team clinicians. The team confirmed International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) diagnoses of childhood autism, atypical autism, Asperger disorder, or pervasive developmental disorder, unspecified.

At the third stage (December 2010 - to October 2015) 17 children diagnosed with: childhood autism, atypical autism or pervasive developmental disorder, unspecified, were included in the study group. For the representativeness of the Study, 27 children with the same diagnosis, age and therapy were added to the study group. All children (44) were receiving intervention of the same type and intensity (applied behavioral therapy, maximum 5 sessions in a week). The dynamics of social and communication development were followed for 36,2 months.

For assessment of the outcomes the optimal outcome (OO) was defined as the critical amelioration of ASD symptoms and improved functioning within the non-autistic range of social interaction and communication confirmed by the multidisciplinary team which were blinded for the baseline data of children.

In all cases behavioral therapy was provided at the same service. Various demographic and clinical data were obtained. The Autism Diagnostic Observation Schedule (ADOS) (Lord & Rutter, 2012) the Vineland Adaptive Behavior Scales—Second Edition (Vineland II) (Sparrow & Cicchetti, 1985), the validated version (Zirakashvili et al., 2018) of the Ages & Stages Questionnaires, Third Edition (ASQ-3) (Squires et al., 2009) and the Wechsler Preschool and Primary Scale of Intelligence - WPPSI-III (Wechsler, 2003) tests were provided by qualified professionals. .

The WPPSI-III is an individually administered IQ test for children aged two years six months to seven years three months (Wechsler, 2002). The test is divided into two age bands, the younger band covering the ages of 2:6–3:11 and the older band covering from 4:0 to 7:3. The WPPSI-III conceptualizes intelligence as a hierarchical structure with different specific abilities comprised in broad cognitive abilities. The conceptualization also postulates an underlying global aspect of intelligence (Wechsler, 2004). Initially, the WPPSI was developed without referring to theoretical foundations of intelligence, but the WPPSI-III was designed to tap more specific theoretically based abilities. That said, the WPPSI-III is not explicitly based on CHC theory, even if this instrument is strongly supported to measure a child's level of g (Lichtenberger & Kaufman, 2004). This instrument provides an overall estimate of IQ, called the full-scale IQ (FSIQ), and composite scores for the different subscales of specific domains of intelligence. For both age bands, there are scores for the Performance IQ (PIQ), Verbal IQ (VIQ), and General Language Composite (GLC). For the older age band, there is also a subscale for Processing Speed (PSQ) (Gordon, 2004; Wechsler, 2002). The FSIQ comprises four core subtests for the younger age band and seven core subtests for the older age band. The PIQ comprises two subtests (Block design and Object Assembly) for the younger children and three subtests (Block design, Matrix Reasoning, and Picture concepts) for the older children. The PIQ measures fluid reasoning, spatial processing skills, attentiveness to detail, and visual-motor coordination skills (Wechsler, 2002).

Results

At the first stage of the study (from January 2009 to February 2010) target population were children aged 2 to 4 years (born between January 1, 2006 and December 31, 2008) who were registered at the primary health care centers of three districts of Tbilisi: Vake, Saburtalo and Dighomi (2651 children). 2044 (77.1% of total sample) children have underwent the screening assessment. Out of total number of screened, 1019 (49.85%) were boys and 1025 (50.14%) were girls.

Each family doctor screened children registered at their working area with the Ages and Stages Questionnaire (ASQ) involving parents of these children in the process. Before the screening all of them were trained in providing screening with use of ASQ. Children whose scores were below the cutoff (56 children) for more than two domains were considered as a risk group. The most frequent were cases with scores below the cutoff in one domain - 6.57%. 3.06% of children had problems in two, 0.88% - in three and 0.55% - in four domains. Only 0.05% of children's scores were below the cutoff in all five domains.

All children who were screened with ASQ also screened with the Modified Checklist for Autism in Toddlers (M-CHAT). 17 children were identified as risk-group for ASD.

At the second stage diagnostic assessment were conducted with the children of the risk group. Diagnostic tools: Autism Diagnostic Observation Schedule (ADOS), Autism Diagnostic Interview (ADI-R), and The Vineland Adaptive Behavior Scale (Vineland II) were used for this purpose. Final diagnosis was made by the multidisciplinary team including family doctors, child neurologist, child psychiatrist, psychologist, and speech and language therapist.

Neurodevelopment disorders were evident in 3.07% and ASD - in 0.876% in children aged 2-4 years.

The following risk factors were identified as statistically significant for confirmed cases of ASD:

- Gender - most were males 15 (93.75%) and only one was a female - 1 (6.25%) ($p<0.0005$).
- Family income – less than 500 GEL ($300), ($p<0.001$).

- Place of residence – most of children of ASD were lived in more developed districts of Tbilisi, Vake or Saburtalo (six cases in each, total 12). Only four cases were from Dighomi. Vake/Saburtalo/Digomi were as 6/6/4 ($p<0.05$).
- Family status – most cases were from nuclear, traditional family and only one was from single parent family, 15 (93.75%), and 1 (6.25%), respectively ($p<0.005$).
- Parents education – prevailed children of parents with high school education, 11/68.75% ($p<0.05$).

In the study group minimal age of confirmed autism diagnosis was 35 (±4.8) months.

At the third stage of the study additional 28 children were enrolled with the same age group and diagnosis of ASD.

All these (44) children have received treatment of the same intensity (applied behavioral analyses therapy, maximum 5 sessions in a week, Tet a Tet treatment: behavioral therapist and the patient) and followed up about 36.2 months (SD 2.5; min – 21; max - 36).

Among these 44 children, 36 (82%) were male and remaining 8 (18%) female. Mean age of children was 5.96 years (SD 1.34 years; min-1.8, max-9.9). Mean age at diagnosis was 37.9 month (SD 12.2 month; min-19, max-72). Anthropometric characteristics of children at birth were as follows: mean length 50.9 cm (SD 1.96 cm; min-44, max -56), mean weight 3.42 kg (SD 0.53 kg; min-2.0, max -4.75).

From the total study group of 44 children (16 from the first stage and 28 additional group) mean age of mothers at delivery was 27.5 years (SD 5.6 years; min-18, max-41) and mean age of fathers at delivery was 31.1 years (SD 5.9 years; min-21, max-45). Median gestation age of the patients was 40 weeks (IQR – 1.25 weeks; min-34, max-42).

Median number of pregnancies at the time of assessment was one (min - 1, max - 6), median number of deliveries was one as well (min-1, max-3). In 26 (59%) cases delivery was without any problem, in 15 (34%) caesarian and in remaining three (7%) cases pathological delivery was reported. Twenty-eight (64%) children's mothers and/or fathers have university education.

In nearly half of mothers some degrees of health problem have been detected during pregnancy. Among them in four cases – low-grade fever, in three cases - arterial hypertension and in another three cases toxicosis in early pregnancy were revealed. Two mothers were prescribed with levothyroxine during pregnancy.

29 (66%) of children were diagnosed with childhood autism - F84.0 (ICD – 10) and remaining 15 (34%) individuals with pervasive developmental disorder, unspecified F84.9 (ICD – 10).

There was no association between outcome and maternal and/or perinatal variables as well as with parent's demographic characteristics.

The diagnosis - Pervasive developmental disorder, unspecified (F84.9) were more frequently associated with better outcome (Pearson chi-square 13.4; df – 1; p=0.001). Children with the diagnosis - pervasive developmental disorder, unspecified (F84.9) (ICD - 10) showed four times increased probability of better outcome compared to those diagnosed with the childhood autism - F84.0 (ICD - 10) (RR 4.22; 95% CI 2.4 – 7.5).

Follow up assessment and Optimal Outcome (OO)

Mean follow up time was 36.2 month (SD 2.5; min – 21; max - 36). At the end of the study six (14%) children showed significant improvement in their social and communicative abilities to normal age range. Clinical assessment of psychiatrist confirmed that those cases were not met with diagnosis of ASD anymore. Those six cases further were considered as cases with OO. Table 1 provides more data on various characteristics of OO cases.

Table 1. Anthropometric and neurocognitive characteristics of children with OO.

#	Sex	Age at diagnosis (month)	ICD 10	ADOS - baseline	ADOS - follow-up	Full scale IQ	PIQ	VIQ	Birth weight (gr)	Length at birth (cm)
1	Male	25	F84.9	16	5	-	-	-	3200	50
2	Female	34	F84.9	19	11	-	-	-	3000	50
3	Female	27	F84.9	14	9	-	-	-	2450	47
4	Male	42	F84.9	16	7	83	90	81	3600	51
5	Female	37	F84.9	9	4	85	93	81	3600	51
6	Male	40	F84.9	9	6	81	84	81	3800	52

ICD 10 – International Classification of Diseases, 10th revision; ADOS - Autism Diagnostic Observation Schedule; IQ – Intelligent Quotient PIQ - nonverbal intelligence performance IQ; VIQ – verbal IQ;

Early Development and Adaptive Behavior

The Ages and Stages Questionnaire (ASQ) assessment was performed in 39 cases. 38 cases (86%) had below cut-off score in communication domain, nine (25%) cases - in gross motor, 17 (39%) cases - in fine motor, 32 (73%) cases - in problem solving and 34 (77%) - in personal-social domains.

We found that fine motor performance was significantly better among individuals with OO, where all six children performed above the cut-off value, when 17 (52%) cases with unfavorable outcome performed below cut-off (Pearson chi-square 5.48; df – 1; p=0.027); Fine motor task performance above the cutoff value was two times more likely to achieve OO compared to those who performed below the cutoff (RR 2.1; 95%CI 1.4 – 2.9).

Vineland II test was performed in 38 cases. Overall, there were significantly low scores in communication - 29 cases (76%), socialization – 23 cases (60%), and maladaptive behavior - 17 cases (44%). Vineland II domains scores were not significantly meaningful predictor for OO. For more details see table 2.

Table 2. Vineland II scores of 38 individuals by domains

Domains	Low	Moderately low	Adequate
Communication; n (%)	29 (76)	8 (21)	1 (2)
Daily living skills; n (%)	7 (18)	19 (50)	12 (31)
Socialization; n (%)	23 (60)	14 (36)	1 (2)
Motor Skills; n (%)	7 (18)	9 (23)	22 (57)
Maladaptive Behavior; n (%)	17 (44)	19 (50)	2 (5)

Neurocognitive assessment

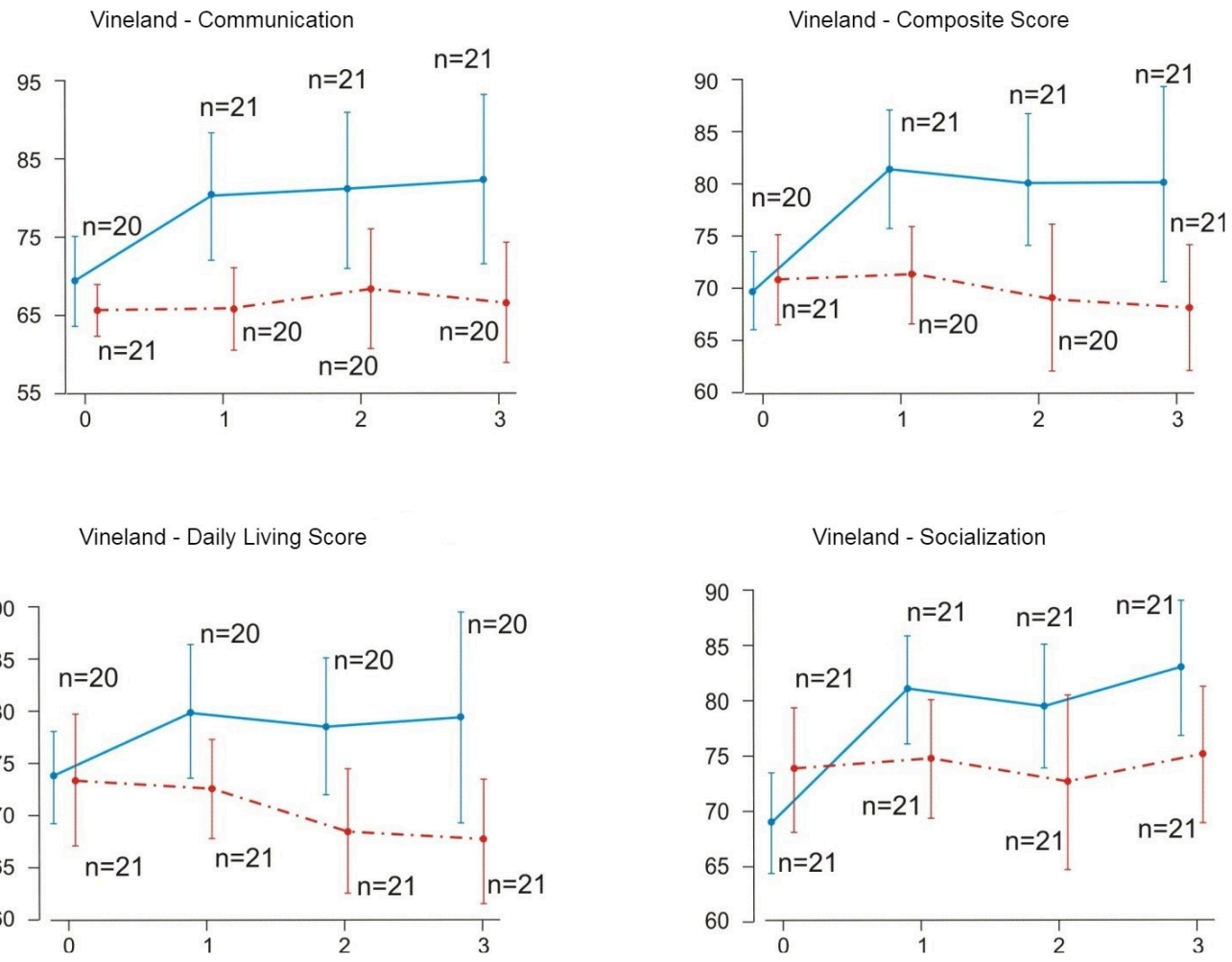
At the diagnostic assessment 28 (64%) cases had their first words. Mean age of the start of first words was 27.2 month (SD 12.6; min – 12, max - 53). Cases with OO started to speak their first words almost nine months earlier compared to those with no improvement; however, this difference was not statistically significant. In all cases some degree of speech and language development problems was noticed at the follow up assessment. Among 12 (43%) of them deterioration of language development was notable compared to baseline level, but without significant difference between groups with and without OO. All six cases (100%) with OO had achieved phrase or fluent speech. From children without favorable outcome only 17 (45%) cases showed similar abilities. This association was statistically significant (Pearson chi-square 6.34; df – 1; p=0.022). The risk of achieving OO was two times higher among children with good verbal abilities (fluent or phrase speech) compared to those with poorer (no speech or single words) verbal performance (RR 2.2; 95%CI 1.6 – 3.2).

Echolalia was notable in 22 (50%) of children. Presence of echolalia was associated with worsening of ADOS communication and social interaction combined score (p=0.019), however echolalia was not associated with OO (for detailed information see the Annex below).

Social smile at follow up assessment was noted in 27 (61%) of cases. Follow up social smile (no + rarely vs. often or always) was associated with improved performance regarding ADOS social interaction and communication total score (p=0.04). However, social smile in the follow up assessment was not associated with OO.

Expression of empathy at baseline was slightly more often observed in persons with OO with no statistically significant association, however at the follow up assessment in all six cases with OO empathy was presented compared to 14 (42%) individuals without favorable outcome; association was statistically significant (Pearson chi-square 6.74; df – 1; p=0.02). Children that exhibited empathy at the follow up assessment showed more than two times increased probability of achieving OO compared to those without such ability (RR 2.4; 95%CI 1.6 – 3.5).

Graph 2. The dynamics of indicators of different areas of Vineland between intensive intervention (blue) and control group (red) according to years.



Full scale IQ by Wechsler Preschool & Primary Scale of Intelligence was assessed in four children with ASD. Mean score was 80.3 (min – 72, max - 85). Performance IQ (PIQ) was assessed in 11 cases, mean score was 93.2 (SD 17.4; min 65, max 121). Verbal IQ (VIQ) was assessed in 5 persons, mean score was 80.2 (SD 3.7; min 74, max 84). In remaining cases assessment of IQ scores were not feasible due to child uncooperativeness or not following instructions. Table (N3) below caries grouped information on variables of interest in terms of association with OO.

Table 3. The summary of factors tested for associations with the OO

Variables	Children with OO	Children without OO	p value	RR (95% CI)
Diagnosis F84.9 (ICD - 10); n (%)	6 (100)	9 (24)	0.001	4.22 (2.4 – 7.5)
Mean age at the start of speaking (months); Mean (SD)	19.8 (8.6)	28.5 (12.8)	n/s	n/a
Fine motor task performance above the cutoff; n (%)	6 (100)	16 (48)	0.027	2.1(1.4 – 2.9)
Social smile at follow up; n (%)	4 (67)	24 (63)	n/s	1.1 (0.3 – 3.7)
Echolalia; n (%)	4 (67)	18 (47)	n/s	0.71 (0.4 – 1.4)
Fluent or phrase speech; n (%)	6 (100)	17 (45)	0.022	2.2 (1.6 – 3.2)
Empathy at the follow; n (%)	6 (100)	14 (42)	0.02	2.4 (1.6 - 3.5)

RR – Risk Ratio; CI – Confidence interval; n/a – not applicable; n/s – not significant.

Interpretation/Discussion

Autism spectrum disorders (ASD) are a diverse group of conditions, characterised by some degree of difficulty with social interaction and communication. Other characteristics are atypical patterns of activities and behaviours, such as difficulty with transition from one activity to another, a focus on details and unusual reactions to sensations (WHO, 2022). ASD imposes a heavy economic burden on society and the patients' families (Gordon-Lipkin et al., 2018), as persons with ASD require considerable care, demanding significant financial resources.

Epidemiological research show an increasing tendencies in the annual prevalence of ASD. Besides the true increase in the prevalence of ASD, there are different other reasons, such as a broader definition of ASD, changes in diagnostic criteria and screening tools, shifts in research methods, and increased awareness of ASD, have been suggested to contribute to this phenomenon (Durkin et al., 2017].

This was the first epidemiological study using gold standard instruments for diagnosis of ASD - pioneering work for Georgia. The prevalence of ASD for that time was 0.876%, what was in concordance with data from other countries. The average prevalence of ASD in Asia, Europe and North America is estimated at 1% (Chiarotti et al., 2020, Fombonne, 2020). In the different findings by years, regarding international prevalence, the World Health Organization in 2018, is estimated that 0.62% of the world's children had ASD. Other systematic reviews of prevalence studies internationally have produced similar summary estimates of approximately 0.7% (Baxter et al., 2015; Elsabbagh et al., 2012), though a review in China reported lower estimates (Wan, et al., 2013). The highest recent international prevalence estimate was 2.64% for 7- to 12-year-old children in South Korea in 2005–2009. This estimate was based on a two-stage screening-confirmation approach (Kim et al., 2011). National registries in Scandinavian countries provide a unique resource for estimating temporal trends. In 2011, ASD prevalence based on registry estimates exceeded 1% in Finland and Sweden and 1.5% in Denmark. These 2011 estimates reflect steady increases in age-specific ASD prevalence across birth year cohorts from 1990 to 2007 (Atladottir et al., 2015), mirroring reports in the United States (Christensen et al., 2016). In Sweden, much of

the increase was attributed to improved documentation and, as seen in the CDC data, identification of milder ASD (e.g., without accompanying intellectual disability) (Idring et al., 2015).

From the Autism and Developmental Disabilities Monitoring (ADDM) Network(USA) recently provided evidence that ASD prevalence per 1,000 children aged 8 years varied across the 11 ADDM Network sites, ranging from 16.5 in Missouri to 38.9 in California. The overall ASD prevalence estimate was one in 44 children aged 8 years. These estimates are higher than ADDM Network ASD prevalence estimates from previous surveillance years (Maenner., et al, 2021).

The latest estimates of the prevalence of ASD worldwide, was published in 2021 by systematic review. A median prevalence of 100/10,000 (range: 1.09/10,000 to 436.0/10,000).

The median male-to-female ratio was 4.2 (Maenner., et al, 2021). In our study the ratio was higher (15), which could be explained by cultural specificity of Georgia – girls should be shyer and more reserved than boys and receive less attention from parents.

Children living in neighborhoods where incomes are low and fewer adults have bachelor's degrees are less likely to be diagnosed with autism spectrum disorder compared to kids from more affluent neighborhoods (Durkin et al.,2017). The economic disrepancy, according information about family income – less than 500 GEL ($300), ($p<0.001$) - was confirmed in our study. Also, most of children of ASD lived in more Central districts of Tbilisi, Vake or Saburtalo (six cases in each, total 12). Only four cases were from Dighomi. Vake/Saburtalo/Digomi were as 6/6/4 ($p<0.05$).

In the study group minimal age of confirmed autism diagnosis was 35 (±4.8) months. From other research between 1990 and 2012, the global mean age at diagnosis of autism spectrum disorder ranged from 38 to 120 months (Daniels & Mandell, 2014). Measures have since been introduced to reduce the age at ASD diagnosis, but the current global mean age is unknown. According to the new research of Maarten Van 't Hof and colleagues (2020), by the review and meta-analysis reports from studies published between 2012 and 2019 (1150 articles, including 56 studies) the mean or median age at diagnosis across 40 countries (n = 120,540 individuals with autism spectrum disorder) was 60.48 months (range: 30.90–234.57 months). The subgroup analysis for studies that only included children aged ⩽10 years (nine studies, including 26 cohorts from 23 countries, n = 18,134 children with autism spectrum disorder)

showed a mean age at diagnosis of ASD - 43.18 months (range: 30.90–74.70 months). Continued efforts to lower the average age at autism spectrum disorder diagnosis are needed. Hypotheses linking factors that increase the likelihood of developing autism with variations in prevalence will require research with large, representative samples and comparable autism diagnostic criteria and case-finding methods in diverse world regions over time. Reliable prevalence data from developing countries are still sparse, and despite growing interest over the past decade, formal study of the influence of global cultural variations on ASD awareness and diagnosis remains limited (Elsabbagh et al., 2012; Zaroff et al., 2012).

With ASD rates on steady increase, the scientists are more and more interested in uncovering the factors linked with this condition, but also with the optimal outcomes.

The severity of co-occurring cognitive impairment is variable and ranges from severe intellectual impairment to above average cognitive ability (Charman et al., 2005). Adaptive skills at school or at work or in social relations usually fall far short of the level corresponding to the individual's intellectual abilities. Nevertheless, there is sometimes rapid improvement in response to intensive treatment, during which the individual's level of social and academic functioning reaches near-typical levels (Anderson et al., 2014; Fein et al., 2013).

Indicators of Optimal Outcome

Our study is the first effort to investigate the clinical, demographic and neurodevelopmental characteristics of ASD in Georgia and discuss these variables in terms of predicting optimal outcome. It is well known that a certain proportion of individuals with ASD may lose the symptoms characteristic of the disorder and thus be removed from the diagnosis of ASD. According to different data, the number of such cases varies from three percent to 25% (Helt et al., 2008). However, the outcome is quite variable between the data of different studies and depends on the duration and intensity of the intervention.

According to our data, by the end of the study, in six cases (14%) the symptoms improved significantly and the optimal solution was observed. The social and communication skills of these patients returned to the typical range, which was finally confirmed by psychiatric

functional evaluation as well. Our data are congruent with the results of studies whose goal was to assess the outcome of ASD (Fein, Dawson)

The variability in ASD outcomes is one important challenge that prompts researchers to identify and investigate predictors that may be associated with the optimal outcome of the condition. Not infrequently, the target of researchers is to search for various genetic factors. This is partly due to the fact that the search for other etiological factors did not yield significant results. The possible genetic underpinnings of autism are highly variable, and there is very little correspondence between genetic alterations and the phenotype of the disorder (Rapin, 2014; Waterhouse, 2013). Other biological markers were also not found to be reliable predictors, which would allow us to estimate in advance the likely solution to the situation. Against this background, the study of behavioral predictive markers turned out to be more promising, and the attention of the scientific community was also mobilized in this regard. According to various studies, a better outcome of the diagnosis in the preschool contingent with ASD is observed in the presence of relatively mild symptoms of autism and high cognitive functioning (Charman et al., 2005; Eaves & Ho, 2007), as well as moderately expressed social deficits (Ben-Itzchak & Zachor, 2007), with better performance in speech and attention (Bono, Daley, & Sigman, 2004; Magiati, Charman, & Howlin, 2007). Imitation skills developed during play were also significant predictors of a successful outcome (Sallows & Graupner, 2005; Vivanti, Prior, Williams, & Dissanayake, 2014).

It should be noted that some individuals, despite the marked symptoms of autism, progress rapidly and achieve a fairly high level of social interaction and independent functioning. In most cases, the mentioned phenomenon was revealed in connection with high socio-economic status, which gives rise to the opinion that the positive effect was related to early and effective intervention. A rapid improvement in ASD symptoms during the first 3-12 months after the start of the intervention is associated with a better outcome (Sallows & Graupner, 2005), more specifically, a rapid improvement in stereotypic behavior by the patient's 2-3 years of age is associated with a favorable outcome (Anderson et al., 2014).

A diagnosis of pervasive disorder unspecified (F84.9) was associated with an improvement in the ASD score in several studies. Similar results were obtained in a study by Helt and colleagues (Helt et al., 2008), where the mentioned diagnose were significantly more likely to achieve an optimal outcome compared to those diagnosed with childhood autism (Sutera

et al., 2007). This is in agreement with the data obtained from our research, where in the case of all six individuals with an optimal outcome, the diagnosis was the pervasive disorder unspecified.

A growing body of evidence is accumulating regarding the importance of early intervention in individuals with ASD. It is clear that early intensive rehabilitation significantly increases the chances of an optimal outcome in individuals with ASD (Cohen, Amerine-Dickens, & Smith, 2006a; G. Dawson et al., 2010; Lovaas, 1987; Sallows & Graupner, 2005). From this point of view, early identification of cases of autism spectrum disorders is of particular importance (Anderson et al., 2014). M-CHAT is one of the successfully used tests for early diagnosis of ASD. The Georgian adapted version of the questionnaire was used within our research. The analysis of our M-CHAT assessment in children with ASD revealed a fairly high level of sensitivity of the test - 97.5%. This means that the Georgian version of the questionnaire correctly detects more than 97% of children with ASD.

The fact that early intervention in the case of ASD is a predictor of a favorable outcome of the condition itself raises the demand for diagnosing ASD as early as possible. According to the recommendation of the American Academy of Pediatrics, developmental screening should be performed at 9, 18, and 24 (or 30) months of age, and autism-specific screening should be performed at 18 and 24 months (Johnson, Myers, & the Council on Children with Disabilities, 2007). However, one of the main problems is the incomplete implementation of this recommendations at the level of primary healthcare. It was found that only 17% of pediatricians follow the APA recommendations. The reason for this may be the lack of awareness of specialists about ASD issues (lack of information about effective autism management capabilities or early diagnosis methods), and it is also possible that specialists deliberately avoided focusing on ASD problems in order to evade dissatisfaction from parents (Barton, Dumont). -Mathieu, & Fein, 2012; Dosreis, Weiner, Johnson, & Newschaffer, 2006).

According to some researchers, ASD screening at 18 and 24 months of age is quite accurate. Modified Checklist for Autism in Toddlers–Revised (D. L. Robins, Fein, Barton, & Green, 2001)] is a flexible screening tool with high sensitivity, meaning that screening will detect most cases of ASD (Khowaja, Hazzard, & Robins, 2015). However, there is a question about the specificity of the questionnaire, and especially in terms of the number of false positive

cases, which can become a source of non-targeted costs and unnecessary burden of human resources. The specificity of the questionnaire was not studied within our research. This requires an assessment with a screening tool among representatives of the healthy population and further determination of the proportion of negative screening results. This is a shortcoming of the research presented by us, however, determining the specificity of the Georgian version of M-CHAT is completely possible and is a future research task. It should also be noted that individuals with a false-positive M-CHAT result (meaning that the subject does not have an autism spectrum disorder, but have symptoms that lead to a false-positive result of the questionnaire) are more likely to have a neurodevelopmental disorder. Any other condition likely to require early detection and intervention (Diana L. Robins et al., 2014). A special problem for the early detection of ASD is those cases which initially show very mild signs of ASD, or experience regression of development by the age of three years. Obviously, in such cases, screening at the 12th and 24th months will not yield results. Therefore, it is necessary to carry out additional screening at a later age, which will allow maximum detection of children with ASD.

Considering the parameters obtained as a result of our research, it is desirable that the Georgian version of M-CHAT is a research tool with high specificity, and it is advisable to implement it in primary healthcare facilities and popularize it among family doctors, which will significantly increase the detection rates of ASD cases.

After ASD screening procedures, it is necessary to have reliable and accessible diagnostic criteria, according to which the final clinical diagnosis will be established. This has an impact on the timely detection of ASD cases and ultimately on the implementation of early intervention issues. Currently, there are different diagnostic systems with different criteria for diagnosing ASD.

The most widely used in the USA is the Diagnostic and Statistical Manual and its latest version, DSM-5 (American Psychiatric Association & American Psychiatric Association, 2013). According to the latter system, the diagnostic criteria for ASD have become relatively stricter, which requires more pronounced symptomatology of pervasive disorder, stereotypic behavior, and restricted interests compared to earlier versions. This created certain problems in terms of comparability of studies conducted at different time periods. In addition, several authors attempted to adapt the research produced in the fourth revision to the criteria of the

new edition. Individuals with relatively mild ASD symptoms were found to no longer meet inclusion criteria (Barton, Robins, Jashar, Brennan, & Fein, 2013; Christiansz, Gray, Taffe, & Tonge, 2016; McPartland, Reichow, & Volkmar, 2012). This creates a certain problem in terms of identifying individuals with a relatively mild form of ASD and implementing their timely intervention, which is highly likely to significantly improve the patient's clinical outcome and quality of life (Moulton, Barton, Robins, Abrams, & Fein, 2016). The 10th revision of the ICD-10 (ICD-10, 2011) developed by the WHO is a diagnostic system that is widely used around the world except the USA. The authors decided to retain the category of atypical autism for cases where standard criteria are not fully met due to age or clinical features.

Another diagnostic system, which mainly maintains the criteria of DSM-5, but also introduces additional developmental characteristics, is called Early Atypical ASD (Zero to Three Organization, 2016). The latter is aimed at diagnosing children aged 9 to 36 months who do not fully meet the ASD diagnostic criteria. Some researchers advocate starting intervention for children who are at risk for developing ASD but do not meet DSM-5 criteria (Soto, Giserman Kiss, & Carter, 2016). According to them, it is appropriate to develop a wider diagnostic criterion for ASD, which ensures the earliest possible diagnosis of children with ASD and subsequent timely full-fledged intervention.

In the case of our study, diagnosis is based on ICD-10 criterion, as in Georgia for that time (2009-2010) and until now the main used classification system was ICD-10.

Another important question to be asked concerns the intervention that should be implemented with individuals with ASD. It is possible that early intervention and maturation of the brain contribute to the normalization of neuronal connections and improvement of the anatomical or functional state of the brain. This opinion is supported by the results of the study by Dawson and colleagues, where the normalization of electroencephalographic parameters of cortical activation was seen under the conditions of early intervention (Early Start Denver Model intervention) (Dawson et al., 2012).

The next step after screening and diagnosing ASD is to implement effective treatment measures. In general, transferring the modern achievements of autism treatment into practice and ensuring its wide availability is quite problematic. Incorporation of evidence-

based, effective intervention methods into daily practice by relevant institutions is a fairly lengthy process.

Access to services is a serious problem related to the management of ASD. Interventions that are effective in well-organized controlled centers may not be available or difficult to implement in community centers. It is desirable to develop a methodology that can be implemented in most rehabilitation facilities (Dingfelder & Mandell, 2011).

In the early days of Autism, this diagnosis was considered an incurable condition. However, a study by Lovaas completely changed this view (Lovaas, 1987). According to his data, half of the patients under observation were involved in the regular educational process and reached an adequate intellectual level. It should be noted that intensive rehabilitation sessions was carried out with these children, which means 40 hours per week for at least 2 years. Moreover, these gains were quite stable during the subsequent multi-year follow-up period.

Cohen and colleagues replicated the Lovaas model and conducted a prospective cohort design study in which children with ASD were followed under two different treatment models. Replication of the Lovaas model involved the following: 35-40 hours of intervention per week, delivered by a specially trained team; parents were trained and further involved in the rehabilitation process (Cohen, Amerine-Dickens, & Smith, 2006b). Some of the individuals in the study received early intensive behavioral (EIB) treatment, while the other group received services through a local school program. ASD diagnoses were assessed by certified neuropsychologists using the ADI-R (Autism Diagnostic Interview-Revised) test, IQ was greater than 35 as estimated by the Bayley Scales of Infant Development-Revised (BSID-R). Baseline demographic or cognitive-behavioral data of the study and control groups did not statistically differ from each other.

Another important difference was revealed in terms of indicators of involvement in the educational process, in particular, the children of the EIB group were more integrated in the educational process. However, it should be taken into account that the mentioned association is biased, since the child's involvement in the educational process is largely determined by the attitude of the parents and the policy of the educational institution.

The full cohort of the study presented by us was subjected to a course of intensive early intervention performed at the level of a tertiary center by qualified specialists. It should also

be noted that the methodology and duration of the intervention were fairly similar for all individuals included in the study, therefore, the power of the estimated effect on the optimal outcome should be similar between individuals, which minimizes the possibility of bias.

Treatment based on applied behavioral analysis is most effective in terms of promoting communication, social interaction, and reducing interfering behaviors. Developmentally oriented and "natural" interventions are increasingly being used, which involves the use of patient-specific natural motivational factors (Schreibman et al., 2015). In general, behavioral therapy is most effective in the earliest possible stages of autism. Earlier onset of intervention is associated with marked improvement in verbal skills. According to various studies, children with ASD who started behavior-based intervention by age 2, 3, or 4 showed reliable improvements in social adjustment and communication skills, with the most impressive improvements in the younger cohort.

A study was conducted comparing 12-15-month-old children with ASD with severe symptoms of autism who received early treatment with the Early Start Denver Model and compared the outcomes of children with ASD whose symptoms were relatively mild compared to the study group, and whose parents also refused intensive rehabilitation /abilitation. According to the results of this study, the children who received intensive intervention had significantly less developmental delay and less symptoms of ASD compared to the untreated group. It is worth noting that of the seven children who received treatment, after repeated evaluations autistic symptoms were noted in two cases. In addition, children with optimal outcomes were found to do better in cases with more hours of treatment. This association was significant in children aged 2-3 years, according to the results of this study. In addition, another prospective study found that during the follow-up period, those patients who maintained optimal outcome rates underwent more intensive and long-term behavioral rehabilitation for ages 2 to 3. It should be noted here that early ASD therapy is closely related to socioeconomic status and availability of intensive intervention. In the United States, ASD is diagnosed, on average, at age four. This rate is even worse among people with low socio-economic status and among minorities (Dawson et al., 2010). According to our study, the mean age of intervention initiation is consistent with the results of this publication. We believe that the optimal outcome rate is largely determined by the intensive intervention and the age range where the intervention is most effective.

According to the first prospective study conducted by Rutter and colleagues, 1.7% of the study group achieved an optimal outcome (Rutter, 1970). About 30 years later, another study found that 17% of respondents had a marked improvement in ASD symptoms (M. Sigman et al., 1999). The possibility of a positive outcome of ASD was later confirmed by other studies, moreover, the individual's high IQ (Patricia Howlin et al., 2004; Szatmari, Bartolucci, Bremner, Bond, & Rich, 1989) and the diagnosis of Asperger's syndrome were named as predictors (Cederlund et al.., 2008).

Very interesting data were obtained from the study of Fein and colleagues, where they evaluated cohorts with optimal outcome, high-functioning autism and typical development. Variables were controlled for age and sex, as well as nonverbal IQ. Verbal IQ differed significantly between these groups and was approximately seven points higher in OO and typically developing individuals compared to high-functioning autism cases (Fein, Barton, & Dumont-Mathieu, 2017).

The results of the study clearly indicate the possibility of such cases when patients with confirmed ASD no longer have the symptom complex characteristic of autism after a certain period of time, and whose social and communication skills, based on the results of the Vineland and ADOS tests, do not differ from peers with typical development in terms of age, gender and IQ from the data.

According to the results of the same study, autism symptoms in early childhood were milder in the group with OO. Similar findings are presented by other studies. It should be noted that the above refers to social interaction difficulties, not communication difficulties and stereotyped behavior. Some evidence suggests that the presence of stereotyped, repetitive behaviors early in life may be associated with adverse outcomes (Watt, Wetherby, Barber, & Morgan, 2008). Stereotypic behavior is also less likely to improve than social and communication skills (Fountain et al., 2012; Seltzer, Shattuck, Abbeduto, & Greenberg, 2004).

Another important finding is that the IQ of children with OO was higher than average. This is important from the point of view that the criterion for inclusion in the selection of research participants was an IQ score of 77 and above, therefore this result cannot be explained by selection bias. It is likely that with an above-average IQ, a person with ASD

compensates for deficits in some social or communication skills. It is also possible that children with higher IQs had higher levels of parental involvement.

Our data revealed an association between the patient's verbal skills and OO. Fluent or phrased speech was reliably observed more often in individuals with OO. Similar results were reported in another study, where receptive language skills as well as verbal and motor imitation skills were reliably associated with OO (Helt et al., 2008). Children with better verbal development showed better results in terms of learning skills in intensive rehabilitation settings (Sallows & Graupner, 2005). Nevertheless, in most cases, there was still a deficit in grammar use quality in terms of pragmatic or semantic language (Kelley et al., 2006). Similar results were obtained in our study, where most of the study cohort had speech deficits of varying degrees, regardless of the severity of the outcome.

The increase in IQ by 25 points was statistically significantly different from the control group, where the similar data was 14 points. A similar effect was observed in terms of adaptive behavior. Against this background, there was no significant difference in terms of expressive speech and non-verbal cognitive abilities. Similar results were found in other studies, although in Cohen's study the effect of change in IQ was more pronounced.

Another interesting finding was that a significant increase in IQ was observed only during the first year. In subsequent years, the difference in IQ gains was no longer statistically significant between the EIB and standard intervention groups. The reason for this may be the intensive increase of IQ indicators during the first year, and in the following years, although the trend is maintained, the results are not reliably different from each other.

According to some studies, one of the significant predictors of autism outcome is individual characteristics of the mother or clinical and laboratory factors during pregnancy and delivery (Dodds et al., 2011). According to our study, no similar factors were found to be associated with the severity of ASD outcome.

One of the important predictors that has been identified according to the results of various studies is the relationship between OO and motor skills, in particular, children with better motor development are more able to achieve OO (Helt et al., 2008; Sutera et al., 2007). Similar results were obtained in our study, where fine motor skills were significantly more frequent in individuals with OO compared to children with adverse outcomes.

The connection between motor skills and the outcome of ASD is confirmed by many other studies. Of course, the pathophysiological mechanisms that probably determine the relationship between the motor field and the ASD outcome are interesting. Although the cardinal features of ASD are marked deficits in social communication and interaction and repetitive, restricted behavioral features, represented by difficulties in social relationships and communication, recently there is increasing evidence that ASD is also associated with difficulties in motor development. According to the results of one meta-analysis, motor coordination disorders were significantly more pronounced in individuals with ASD compared to representatives of a typically developing control group (Fournier, Hass, Naik, Lodha, & Cauraugh, 2010). A detailed examination of the motor functioning characteristics of individuals with ASD has revealed difficulties in various components of the motor domain, including fine and gross motor skills and postural control (Bhat, Landa, & Galloway, 2011). According to our data, the sub-sphere of fine motor skills was found to be statistically significantly associated with the optimal outcome.

Fine motor skills are a specific part of the motor domain that is often deficient in individuals with autism. Fine motor skills are represented by an individual's ability to perform filigree manipulations of objects, and seem to be the most vulnerable area in individuals with ASD in contrast to general gross motor skills (eg, walking). Deficits in fine motor skills in ASD are quite variable, ranging from difficulty grasping a toy to deficits in hand washing. Children at high risk of developing ASD have deficits in fine motor skills from the first years of life (Estes et al., 2013; Leonard et al., 2014; Libertus, Sheperd, Ross, & Landa, 2014). Moreover, individuals at high risk of developing ASD had significantly more frequent fine motor impairments compared to individuals at low risk of developing ASD. In particular, as a result of a meta-analysis, it was revealed that by the age of about 12 months, there is already a noticeable lag in terms of fine motor skills in representatives of the high-risk group for the development of ASD (Garrido, Petrova, Watson, Garcia-Retamero, & Carballo, 2017).

In another study, in a cohort of children at high risk for developing ASD, there were significantly more marked deficits in fine motor skills in individuals who eventually developed autism compared to those who did not eventually develop ASD (LeBarton & Iverson, 2013).

There is evidence that motor skills are related to the development of skills in areas such as language. In children with ASD, the level of motor skill development during the first two years is a predictor of a high probability of developing expressive language by age 4. (Gernsbacher, Sauer, Geye, Schweigert, & Hill Goldsmith, 2008; Stone & Yoder, 2001). It has also been shown that in individuals with ASD, fine motor skills at 1-2 years of age significantly determine the level of expressive language at 3 years of age (Leonard, Bedford, Pickles, & Hill, 2015). The mentioned data probably indicate that the formation of motor and expressive language fields is taking place at the same time and is closely related to each other. The theoretical basis of this process is the opinion according to which the discovery of new motor skills gives the child more opportunities to master more areas and interact with the environment. This, in turn, facilitates communication with strangers and ultimately promotes the development of language. For example, research has found that a 13-month-old child who can walk shares objects (eg, a toy) with their mother significantly more often than a child of the same age who can sit up (Karasik, Tamis-LeMonda, & Adolph, 2014). In addition, those children who can hold an object in their hands are significantly more likely to share it with their parent or guardian, therefore, the chance of naming this object and acquiring new knowledge/information by the child increases. Accordingly, the development of fine motor skills, in turn, contributes to the formation of interpersonal relationships and the development of language skills.

Given the close relationship between the development of motor and language domains, it is possible to assess the motor skills of children with ASD to predict language development difficulties and to identify individuals at high risk for the development of speech and communication difficulties (Iverson & Wozniak, 2007; Mitchell et al., 2006).

On the other hand, the identification of children who have a high probability of language deficiency allows to plan appropriate targeted intervention at the early stages.

Attention to the development of fine motor skills at an early age is important, because in the case of deficits, early intervention is highly likely to lead to improvement, which in turn will contribute to the development of verbal skills and, as a result, communicative abilities. The results of these studies emphasize the importance of focusing on the development of fine motor skills in children at high risk of ASD, allowing us to conduct early intervention

and optimize the chances of a favorable outcome (Koterba, Leezenbaum, & Iverson, 2014; Libertus, Joh, & Needham, 2016).

Early social relationships in childhood and adulthood emphasize the process of developing social cognition and lead to the formation of more complex social relationships later in life. Under typical developmental conditions, smiling is one of the most frequent social behaviors exhibited during the first 6 months of life (Yale, Messinger, Cobo-Lewis, & Delgado, 2003). The social smile appears at the age of 2-3 months and gradually becomes more intense and charged with a communicative context. Along with the growth of the child's social cognition, along with the smile, the expression of eye contact with the social partner gradually increases (Messinger & Fogel, 2007).

At the behavioral level, a social smile combines two components, it is a facial expression expressing a positive affect and directing the gaze towards the individual towards whom the aforementioned positive affect is expressed. Various studies have shown significant deficits in social smiling in individuals with autism (Swettenham et al., 1998).

There is evidence that social smiling difficulties are more pronounced in children with ASD compared to individuals with typical development. Dawson's study compared the intensity of social smiling and eye contact between children with ASD and typically developing children. Quantitative indicators of positive affect and eye contact were found not to differ significantly between groups, however, in the case of children with ASD, eye contact and positive affect were significantly less used in the context of social interactions (G. Dawson, Hill, Spencer, Galpert, & Watson, 1990). In addition, another study found that deficits in social smiling were more pronounced in children later diagnosed with ASD. Therefore, we may consider social smiling as an early predictor of ASD. Eye contact helps not only to engage in interpersonal relationships, but also to develop social, emotional and language functions, to receive feedback, which ultimately creates a prerequisite for the development of learning processes. Therefore, improving eye contact during the rehabilitation process is likely to increase the chances of a better outcome.

According to the data of our study, the presence of a social smile was noted in 61% of cases by repeated assessment. The presence of social smiling (often or always) was statistically significantly associated with improved ADOS scores, but was not associated with optimal outcome. The reason for this may be the small sample size. Nevertheless, evaluation of social

smiling as a possible predictor of optimal outcome should be done in the study of autism spectrum disorders.

According to our study, echolalia was not associated with better outcome. Similar results have been obtained in other studies, where echolalia was more present in children with autism compared to individuals with Asperger's syndrome (Szatmari, Bartolucci, & Bremner, 1989).

Echolalia is a pervasive verbal phenomenon in children with autism, which in turn represents an automated behavior that lacks communicative function. However, according to some researchers, the echo may have a relational meaning and an individual with autism may use it in terms of communication. In this regard, the research (Sterponi & Shankey, 2014) is interesting, according to which a child with autism may attempt verbal communication through echolalia for different situations.

Children who did not meet criteria of the diagnosis of ASD are included in the optimal outcome group. Studies that describe the subsequent development of individuals with OO are rather small. There are also few such studies, the purpose of which is the long-term observation of patients with OO and the study of the dynamics of development. Table 4 summarizes the results of various studies regarding the stability of the optimal outcome for autism.

Table 4. Long-term outcome of autism spectrum disorders - meta-analysis

Author	*Middle age*	*Diagnosis*	*Sample Size*	*OO (%)*
Rutter et al.	16	Childhood Autism	63	14
DeMyer et al.	12	Childhood Autism	126	10
Lotter	-	Childhood Autism	29	14
Gillberg and Steffenburg	20	Childhood Autism	23	4
Kobayashi et al.	22	Childhood Autism	197	27
Larsen and Mouridsen	-	Childhood Autism	18	28
Engstrom et al.	31	Asperger Syndrome	16	12

		and Autism		
Howlin et al.	29	Asperger Syndrome and High Functioning Autism	67	22
Cederlund et al.	21	Asperger Syndrome and High Functioning Autism	70	27
Eaves and Ho	24	Autism/ Atypical Autism	48	21
Farley et al.	32	Autism/High Functioning Autism	41	49
Esbensen et al.	38	ASD/intellectual Disability	70	11
Gillespie-Lynch et al.	26	Childhood Autism	20	30
Howlin et al.	44	Childhood Autism	60	17

It should be noted that the results of this study show a fairly high rate of optimal outcome even after many years of observation. However, more and more information are being collected that the absence of autism symptoms or their minimal expression is sometimes accompanied by significant psychiatric comorbidity, which prevents the patient, despite the optimal outcome, from fully realizing the achieved progress.

One study, which followed five years of 17 individuals with optimal outcomes, found that 70% had attention deficit hyperactivity disorder (ADHD), and 65% had tics. Meanwhile, none of the patients experienced a relapse of any of the symptoms, characteristic of autism (Zappella, 2010).

Fein evaluated 34 individuals with OO between the ages of 8 and 21. Patients were assessed on various domains of functioning, communication, facial recognition and verbal skills. The obtained data were further compared with data from individuals with typical development (Fein et al., 2013). This study found a high prevalence of ADHD and specific phobias. In another study, where individuals with OO were assessed by structured telephone interview

and who were free of autism symptoms by the age of 4 years, 3 out of 14 cases had a relapse of autism symptoms, and 6 cases had a borderline condition (Olsson et al., 2015).

The study conducted by Mukades and colleagues examined the characteristics of school-age individuals with OO. Several years later, the same cohort was assessed to see how stable the improved status was and whether any other psychiatric symptoms were present (Olsson et al., 2015). According to the results of this study, it was revealed that no case was a relapse of autism symptoms noted, therefore, a favorable outcome was maintained in these individuals for several years. However, according to another study, 29% of children with autism who reached OO by the age of 4 years still had symptoms of autism in late childhood.

The long-term stability of the optimal outcome is still controversial and needs further study. As for psychiatric comorbidity, it was revealed that in 90.2% of cases, patients were diagnosed with different psychiatric disorders at least once in their lifetime, and more than 80% were diagnosed with mental disorders at the time of evaluation. Therefore, although psychiatric problems in individuals with OO gradually decrease over time, it can be said that rates of psychiatric comorbidity remain high.

Therefore, even in cases where an optimal outcome is achieved and an appropriate treatment program for ASD is completed, long-term clinical follow-up of these individuals is necessary for timely identification and management of psychiatric problems. Particular emphasis should be placed on the detection of ADHD, since this comorbidity is most often seen in individuals with ADHD.

There is an opinion that ADHD and autism are different manifestations of dysfunction of the same neurobiological substrate. Research has identified significant neurobiological similarities between autism and ADHD, including clinical and genetic features (Ronald, Simonoff, Kuntsi, Asherson, & Plomin, 2008; Simonoff et al., 2008).

Specific phobia is the second most common comorbidity in patients with autism, which maintains a high prevalence even after achieving optimal outcomes.

Obsessive-compulsive disorders are also significantly present, which was detected in approximately one fifth of the research cases (Mukaddes & Fateh, 2009).

According to the study data, 34 individuals with OO no longer had symptoms of autism, which was confirmed by ADOS testing and clinical assessment. There was no significant difference in ADOS communication and socialization scores for patients with OO compared

to the typically developing group, although seven cases were found to have difficulties in social functioning despite OO, which were associated with problems with anxiety, depression, and impulsivity. From the early history, it is noteworthy that patients with OO had less intense social symptoms compared to the high-functioning autism group, although there was no difference in relation to stereotypic behaviors and expression of communication difficulties.

Although socialization and communication problems are no longer visible in patients with OO, a mild residual deficit can still be observed. Although according to the results of the Vineland and ADOS tests, the OO group did not differ from the typical development group, with more subtle and deeper studies, it is possible to reveal atypical social behavior.

Within the framework of our study, further longitudinal observation of recruited individuals is planned, which, after some time, will allow us to analyze the long-term outcome of individuals with an optimal outcome and to assess how stable the gains they experienced in terms of communication and social interaction progress are. In addition to individuals with an optimal outcome, our focus will remain on those patients whose outcome was not favorable and who remained diagnosed with ASD. Regarding this group, the dynamics of development of the disorder, the course of development of social and communication skills will be very important.

Research Limitations and Difficulties

The study was conducted on a relatively small cohort, which may have affected the power of the study, making it less likely than desired to detect associations that actually exist in the population. In addition, the study cohort represented patients from a tertiary center where early intensive intervention and correct diagnosis were provided, which may have led to higher rates of optimal outcome. This should be taken into account when extrapolating research data.

When studying the predictors of ASD, it is necessary to evaluate such variables that reflect the possible influence of environmental factors. Indicators of speech and IQ are difficult to be influenced by rehabilitation measures. Therefore, by modifying the environmental factors, the rehabilitation process of ASD may turn out to be more successful. Farley et al. (2009) Billstedt et al. According to (2011) data, more integration into society leads to a significant improvement in the yield of ASD, more specifically, recreational activity during the day and involvement in social activities will be an important contributing factor in the management of ASD in terms of additional resources.

Conclusions and Recommendations

Conclusions

According to Our Study the prevalence of neurodevelopment disorders was 3.07% and ASD - 0.876% in children aged 2-4 years.

The following risk factors were identified as statistically significant for confirmed cases of ASD:

- Gender - most were males 15 (93.75%) and only one was a female - 1 (6.25%) ($p<0.0005$). The prevalence of ASD was significantly ($p<0.01$) higher among boys than among girls,
- Family income – less than 500 GEL ($300) ($p<0.001$).
- Place of residence – most of children of ASD were lived in central districts of Tbilisi, Vake or Saburtalo (six cases in each, total 12). Only four cases were from Dighomi. Vake/Saburtalo/Digomi were as 6/6/4 ($p<0.05$).
- Family status – most cases were from nuclear, traditional family and only one was from single parent family, 15 (93.75%), and 1 (6.25%), respectively ($p<0.005$).

In the study group minimal age of confirmed autism diagnosis was 35 (±4.8) months (less than of ADDM Network study where the median age of the first evaluation was 44 months).

In 6 (14%) of the 44 patients of the study cohort, regression of autism symptoms, amelioration of speech and language abilities and an optimal were noted. According to our research, the indicators of the optimal outcome of autism spectrum disorders are congruent with the data of international studies;

According to the data of our study, the following significant predictors associated with optimal outcome were identified: PDD-NOS, verbal skills, fine motor skills. The connection of the mentioned factors with the optimal outcome of autism has been confirmed by international studies. In addition to the above-mentioned variables, factors such as social smile and empathy and echolalia led to a statistically significant improvement in ADOS scores, in particular, the presence of social smiles and empathy was associated with the improvement of ADOS-scores, while echolalia was associated with the deterioration of

ADOS-scores. There is evidence from scientific studies that these factors are important predictors for optimal outcome of autism, although our data failed to detect such a connection. The reason for this is probably the relatively small size of the study sample.

Data from various studies agree that early and comprehensive treatment is especially important in terms of achieving an optimal outcome. This is also confirmed by the data of our study, where the treatment was practically carried out at an optimal age, and as a result, quite impressive parameters of a favorable outcome were obtained. The intervention is particularly effective in children under 3 years of age, with improvements less significant at later ages. The above indicates that the role of early detection is paramount. In the case of our study, the intervention was carried out in a tertiary clinic, where high standards were observed, therefore, the percentages of the optimal outcome correspond to the results of studies conducted with a similar design.

For the timely implementation of an intensive comprehensive intervention, it is necessary to develop a valid, highly sensitive screening tool and then to widely use it at the level of primary healthcare. As part of our study, the sensitivity of the M-CHAT-R screening questionnaire was evaluated, and as a result, a sensitivity rate of 97% was revealed. This is quite a good parameter for the screening questionnaire and leads to the correct identification of the absolute majority of cases of autism spectrum disorders.

We definitely consider the continuation of the prospective part of the research and the study of psychiatric co-morbidity, dynamics of social and communication skills in our patient cohort. Also, the most important challenge is to assess the stability of untrained skills in individuals with optimal outcomes through

Recommendations

ASD is an urgent public health concern that could benefit from enhanced strategies to help identify ASD earlier; to determine possible risk factors; and to address the growing behavioral, educational, residential and occupational needs of this population. Much of what we learn everyday about autism spectrum disorder (ASD) is coming from developed parts of the world and very limited data about its prevalence, etiology, clinical picture and treatment interventions come from low and middle-income regions. To our knowledge, the prevalence

of ASD has not been estimated in Georgia or other post-Soviet countries; such information is fundamental to the provision of adequate medical and educational resources for the affected children. Establishing prevalence of ASD in Georgia will help in change policies for persons with ASD, including planning of needed services and professionals to fulfill requirement of all persons with ASD.

Epidemiologic investigation of potentially modifiable risk factors will catalyze further advances in research and public health; improve understanding of the etiology and pathophysiology of ASD as well as pharmacologic and psychosocial interventions for ASD.

Early comprehensive intervention is essential in all cases, because the initial severity of the disease is not related to the possible outcome, and a seemingly severe case may have a chance of a good outcome later on. Because of this, an awareness campaign should be launched to bring autism out of the shadows to ensure early intervention and increase the chance of OO.

Modifiable predictors, activities focused on changing the environment It is important that, although the severity of symptoms according to ADOS scores was quite variable in the optimal outcome group, this did not affect the reliability of the outcome.

This leads us to the need to create centers staffed by high-level specialists, properly equipped, where standardized, early intensive treatment of children with autism will take place, which in turn will be beneficial not only for the specific child and his immediate environment, but also in the future will significantly improve the general situation in terms of public health.

The economic problem should be emphasized here. Due to the high cost of services, according to various studies, children were not able to receive high standard treatment. This is emphasized in many authoritative studies. Despite the possibilities for the autistic children to be involved in some state and Governmental programs which we have in our country, because of increase needs and high prevalence of the disorder it is necessary for the state to prioritize the problem of autism and ensure universal access to treatment with multi-year prospective follow-up.

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