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DEVELOPMENTAL PROFILE OF TODDLERS WITH AUTISM SPECTRUM DISORDER AT A TERTIARY CENTRE IN TURKEY

ÜÇÜNCÜ BASAMAK SAĞLIK HİZMETİ VEREN BİR MERKEZDE OTİZM SPEKTRUM BOZUKLUĞU NEDENİYLE İZLENEN KÜÇÜK ÇOCUKLARIN GELİŞİMSEL ÖZELLİKLERİ

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ABSTRACT

AIM: The aim of the study was to describe the clinical and developmental characteristics of toddlers with autism spectrum disorder (ASD); and find out early manifestations.

MATERIAL AND METHOD: Medical records of 134 ASD diagnosed children under 4 years of age between January 2017-May 2019 were retrospectively reviewed. Developmental characteristics of the children diagnosed at ≤24 months and >24 months of age were compared.

RESULTS: Forty-three (32.1%) of the children were diagnosed with autism at ≤24 months of age, and 91 (67.9%) were diagnosed at > 24 months. The most common concern expressed by parents at admission was language delay (46.2%). While only 1.5% of parents named "autism" spontaneously as a concern at admission, 73.9% of parents expressed concerns about ASD when the history was detailed. Parental concern about ASD (p=0.031) and mothers' educational level >8 years (p=0.002) were correlated with earlier diagnosis. Children diagnosed at ≤24 months of age were more likely to have inability to follow verbal commands (p=0.012) and delayed motor milestones (p=0.008). Other ASD signs and clinical characteristics were similar between children who diagnosed at ≤24 and >24 months of age.

CONCLUSION: The signs of ASD emerge over the first 2 years of life. Children who diagnosed ASD at ≤24 months of age have poorer receptive language and motor skills. Parents recognized the warning signs of ASD, but they might have not express their concerns clearly. Pediatricians should take time to listen the parents' developmental concerns and notice the early symptoms of ASD.

Key words: *Autism spectrum disorder, signs of autism, developmental profile, parental concern, early diagnosis*

ÖZET

AMAÇ: Çalışmanın amacı otizm spektrum bozukluğu (OSB) tanısı alan küçük çocukların klinik ve gelişimsel özelliklerini tanımlamak ve OSB'nin erken belirtilerini araştırmaktı.

GEREÇ VE YÖNTEM: Ocak 2017-Mayıs 2019 tarihleri arasında, 4 yaş altında, otizm tanısı alan 134 çocuğun tıbbi kayıtları geriye dönük olarak incelendi. Yirmi dört aylık ve öncesinde tanı alan çocuklarla, 24 aylıktan sonra tanı alanların gelişimsel özellikleri karşılaştırıldı.

BULGULAR: Çocukların 43'ü (%32,1) 24 aylık ve öncesinde, 91'i (%67,9) ise 24 aylıktan sonra otizm tanısı almıştı. Ebeveynlerin en sık başvuru yakınması konuşma gecikmesiydi (%46,2). Ebeveynlerin sadece %1,5'inin başvuru yakınmalarını kendiliğinden "otizm" olarak bildirdikleri, %73,9'unun ise öykü derinleştirildiğinde OSB ile ilgili kaygılarını dile getirdikleri saptandı. Ebeveynlerin OSB ile ilişkili kaygı bildirmesi (p=0,031) ve anne eğitim süresinin >8 yıl olması (p = 0,002) daha erken tanı ile ilişkili saptandı. Yirmi dört aylık ve öncesinde tanı alan çocuklarda, komut almada zorluk (p=0,012) ve hareket alanında gecikme (p=0,008) daha sıktı. Diğer OSB bulguları ve klinik özellikler ≤24 ay ve >24 ay tanı alan çocuklarda benzerdi.

SONUÇ: OSB belirtileri yaşamın ilk 2 yılında ortaya çıkmaktadır. OSB tanısını 24 aylık ve öncesinde alan çocuklarda, alıcı dil ve hareket işlevlerinde zorluk daha sıktır. Ebeveynler OSB belirtilerini farketmelerine rağmen, endişelerini açıkça ifade etmeyebilirler. Çocuk hekimleri ailelerin gelişim ile ilgili kaygılarını dinlemek için onlara zaman ayırmalı ve OSB'nin erken belirtilerini farketmelidirler.

Anahtar kelimeler: *Otizm spektrum bozukluğu, otizm belirtileri, gelişimsel özellikler, ebeveyn kaygısı, erken tanı*

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This study was conducted in Ankara Child Health and Diseases Hematology and Oncology Training and Research Hospital and ethical committee of approval was obtained from same hospital (Project No:2019-145, Date: 05/28/2019).

INTRODUCTION

Autism spectrum disorder (ASD) is characterized by deficiencies in social communication skills, repetitive sensory-motor behaviors and restricted interests (1). The prevalence of ASD has been increased over the last few decades and reported as 1 in 59 children (2). It is reported that ASD is related to the early altered brain development and neuronal organization, and symptoms initially appear by the first years of life (3, 4). Although parents have concerns related to ASD by the age of 12-18 months, most of children are usually diagnosed between 3 and 4 years of age (2, 5-7). Delay in the diagnosis of ASD is an important barrier for the children access to specialized evidence-based interventions on time that can improve long term outcomes during the sensitive period of brain development (8).

Knowing the early clinical features of ASD will provide timely and appropriate guidance. To the best of our knowledge, there is no study evaluating the developmental profile of toddlers with autism in Turkey. The aim of our study was to evaluate the clinical, developmental and demographic characteristics of toddlers with ASD; and find out early manifestations.

MATERIAL AND METHOD

This retrospective, observational study was conducted in Ankara Child Health and Diseases Hematology and Oncology Training and Research Hospital and ethical committee of approval was obtained from same hospital (Project No:2019-145, Date: 05/28/2019).

Participants.

We included children under four years of age who were newly diagnosed with ASD, followed by both department of developmental-behavioral pediatrics, and child and adolescent psychiatry between January 2017-May 2019. In order to prevent misdiagnoses such as lack of stimuli, attention deficit hyperactivity disorder, children who were evaluated at least 2 different times were included in the study.

Developmental Assessment And Diagnosis.

Developmental assessment included a detailed information with open-ended interview technique with parents about general development of their children, current or past concerns related with ASD, and observation of the child's free play, relationship and interaction with parents and clinician in a playroom on a regular basis. Diagnosis of ASD was performed according to diagnostic criteria of DSM-V (1), and the severity of autistic symptoms was measured using Childhood Autism Rating Scale (CARS) (9). The International Guide for Monitoring Child Development (GMCD) was used to assess the communicative, motor, play, relation and self-help skills of the child (10).

Measurements.

1. The Childhood Autism Rating Scale is a behavioral rating scale used to diagnose and evaluate the severity of ASD (9). It has been showed that CARS distinguishes ASD from non-ASD with good sensitivity and specificity in children between 2 and 4 years old (11). Turkish validity and reliability of CARS was performed (12). Sum scores can range from 15 to 60; scores more than 30 indicate that the child is in the autistic range. Scores between 30-37 are categorized as mild to moderate autism and scores between 37-60 are categorized severe autism (9).

2. The International Guide for Monitoring Child Development, developed in Turkey by Ertem et al (10), provides a method for developmental monitoring and early detection of developmental difficulties in low and middle income countries. The GMCD is a brief, open-ended, preceded interview with the primary caregiver. Delays in each developmental domain were defined as two standard deviations or more below in the relevant area according to GMCD. Expressive language such as forming phrases or pointing, receptive language including follow age appropriate verbal commands, play, relation, motor and self help skills were evaluated according to GMCD.

Procedures.

Sociodemographic information [age, sex, parental age and education (≤8 and >8 years of educational attainment), parental concerns and daily screen time at initial presentation], findings obtained from observation of the child's free play and interaction with parents and clinician, GMCD results, CARS scores, and clinical evaluations (additional chronic diseases, hearing, metabolic and genetic evaluation) were retrospectively reviewed from medical records. Characteristics of ASD symptoms at initial presentation including poor eye contact, echolalia, inability to follow verbal commands, motor stereotype, unusual play, regression, self injury behavior, insistence on sameness, restricted interests, unusual interest in sensory aspects of the environment, self help skills, pretend play, pointing, joint attention, interest of peers, responsiveness to name were recorded. By comparing the clinical and developmental characteristics of children diagnosed at ≤24 months and >24 months of age, the early signs and symptoms of ASD were investigated. Regression is defined by initial period of apparently typical development followed by a substantial loss the skills and stop gaining new skills (13).

Statistical analyses were performed using the SPSS statistical package for MAC (v. 20.0). Categorical variables between groups were analyzed using the chi-squared test. Comparison of mean between two groups was examined using a t-test where the data fit a normal distribution and the Mann–Whitney U test where the data was non-normal. A p value of 0.05 was deemed to indicate statistical significance.

RESULTS

A total of 134 children were enrolled. 80.6% of the children were male. The mean age at diagnosis was 29.6±8.3 months, while it was 28.3 ± 7.8 months for girls and 29.9 ± 8.4 months for boys (p>0.05). ASD diagnosis was performed at ≤18 months, 19-24 months and >24 months of ages in

11 (8.2%), 32 (23.9%) and 91(67.9%) children, respectively. Prematurity was determined in 23.9% of the cases. 29.1% of children were hospitalized in neonatal period and most common diagnosis was indirect hyperbilirubinemia (38.4%). Mean age of mothers' and fathers' were 28.8±5.2 and 32.5±5.6 years, respectively. Eighty (59.7%) of mothers and 89 (66.4%) of fathers had completed >8 years of education. Consanguineous marriage rate was 20.9%. **Table 1** shows demographic characteristics of the children.

Table 1.Demographic characteristics of the study group

Demographic characteristics	Values
Gender, n (%)	
Female	26 (19.4)
Male	108 (80.6)
Age at diagnosis, n (%)	
≤18 months	11 (8.2)
19-24 months	32 (23.9)
25-36 months	59 (44.0)
37-48 months	32 (23.9)
Birth weight, g, (mean±SD)	3071 ± 744
Gestational week, week, (mean±SD)	38.3 ± 2.7
Premature birth (<37 gestational week), n (%)	32 (23.9)
Neonatal intensive care unit admission, n (%)	39 (29.1)
Mothers' age, years, (mean±SD)	28.8±5.2
Fathers' age, years, (mean±SD)	32.5±5.6
Mothers' education, n (%)	
≤8 years	54 (40.3)
>8 years	80 (59.7)
Fathers' education, n (%)	
≤8 years	45 (33.6)
>8 years	89 (66.4)
Employment, n (%)	
Mothers'	25 (18.7)
Fathers'	130 (97.0)
Consanguineous marriage, n (%)	28 (20.9)
Family structure, n (%)	
Nuclear family	115 (85.8)
Extended family	19 (14.2)

Eighty-two (61.2%) of toddlers were evaluated three or more times (mean 3.2±1.5). At referral, according to parent reports, only 3.7% of the children had daily screen time less than one hour, 7.5% had 1-2 hours, 13.4% had 2-4 hours and 75.4% had more than 4 hours screen time.

The most common concerns expressed by the parents at admission were language delay (45.5%), developmental delay (11.9%) and lack of responsiveness to name (9.7%) **(Table 2)**. Thirty-nine (29.1%) families reported concerns related with core symptoms of autism such as lack of responsiveness to name, poor eye contact, poor social interaction, inability to follow verbal commands, motor stereotypies, repetition of words or phrases or noises and covering his ears with hands for blocking out noise at admission. Ten children (7.5%) were diagnosed with ASD during their developmental follow-up due to developmental risks such as prematurity and their parents didn't express any concern. Two parents reported suspicion of ASD spontaneously, 73.9% of parents (n=99) expressed concerns about autism when the history was detailed. Parental concern after history detailed about ASD was associated with earlier diagnosis (27.4±7.6 vs 31.2±9.58, p=0.031).

Table 2. Parental concerns at initial presentation

	n (%)
Language delay	61 (45.5)
Developmental delay	16 (11.9)
Lack of responsiveness to name	13 (9.7)
Poor eye contact	8 (6.0)
Motor delay	6 (4.5)
Poor social interaction	6 (4.5)
Inability to follow verbal commands	5 (3.7)
Motor stereotypies	4 (3.0)
Suspicion of autism	2 (1.5)
Repetition of words, phrases and noises	2 (1.5)
Covering his ears with hands for blocking out noise	1 (0.7)
No concern (diagnosed, during developmental follow-up)	10 (7.5)

The initial clinical characteristics of ASD according to the age of diagnosis are presented in **Table 3**. The most common clinical characteristics in children diagnosed at ≤24 months of age were inability to follow verbal command (100%), lack of responsiveness to name (95.3%) and no index finger pointing (90.7%). Inability to follow verbal commands (p=0.012) and delay in motor milestones (p=0.008) at initial evaluation were more common in children diagnosed at ≤24 months than children diagnosed after 24 months of age. Other ASD signs and clinical characteristics were similar between the age groups.

History of regression was in 32.8% of children and the mean regression time was 16.7±5.7 months. There was no significant difference between the regression rates in boys and girls (39% vs 34.6%, p=0.68). According to GMCD, expressive language, receptive language and motor delay were in 117 (87.3%), 126 (94%) and 44 (32.8%) children, respectively. Delay in relating, play and self-help skills were in 134 (100%), 112 (83.6%) and 82 (61.2%) of children, respectively.

The CARS scores were available for 92 children. The mean CARS score was 43.1±5.2. Eighty-three (90.2%) of toddlers had CARS score in the severe range, 9.8% had scores in the mild/moderate range. There was no difference in the severity of autism between girls and boys (CARS scores for boys 43.2±5.1, girls 43±5.7, p=0.61).

Children of mothers with an educational level of more than 8 years were diagnosed earlier than children whose

mothers' had ≤8 years education (27.7±7.3 vs 32.2±9 months, p=0.002). There was no relationship between the CARS scores of the children and mothers' educational attainment (p>0.05). Fathers' education level was not associated with the age of diagnosis and the severity of ASD (p>0.05).

Microcephaly and macrocephaly were in 6.5% and 6.5% children, respectively. Three children had severe or profound hearing loss. Genetic disease was detected in 10 (13.1%) of 76 children who were examined for genetic disease, and determined genetic diseases were 16p13.11 microdeletion syndrome (n=1), 2q23.1 microdeletion syndrome (n=1), Beckwith Wiedemann syndrome (n=1), tuberous sclerosis (n=2), Down syndrome (n=2), Cornelia de Lange syndrome (n=1), the phosphatase and tensin homolog (PTEN) gene mutation (n=1), and leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (n=1). Two patients had surgery for congenital cataract. The most common additional disability was epilepsy and it was observed in 13 cases (9.7%). Melatonin was given to one patient due to sleep problems. Inherited metabolic disease was not detected in any of 87 children who were tested for inherited metabolic diseases.

Table 3. ASD signs and clinical characteristics according to diagnosis at ≤ 24 or > 24 months of age

	Total (n=134) n (%)	Diagnosis at ≤24 months of age (n=43) n (%)	Diagnosis at >24 months of age (n=91) n (%)	p value
Echolalia	28 (20.9)	6 (14)	22 (24.2)	0.128
Inability to follow verbal commands	123 (91.8)	43 (100)	80(87.9)	**0.012**
Lack of pretend play	99 (73.9)	33 (76.7)	66 (72.5)	0.383
No index finger pointing	113 (84.3)	39 (90.7)	74 (81.3)	0.126
Lack of joint attention	116 (86.6)	38 (88.3)	78 (85.7)	0.432
Motor stereotypies	105 (78.3)	35 (81.4)	70 (76.9)	0.352
Unusual play	116 (86.6)	38 (88.3)	78 (85.7)	0.441
No peer play	106 (79.1)	37 (86)	69 (75.8)	0.177
Poor eye contact	121 (90.2)	37 (86)	84 (92.3)	0.206
Lack of responsiveness to name	125 (93.2)	41 (95.3)	84 (92.3)	0.396
Self injury behavior	24 (18)	7 (16.2)	17 (18.6)	0.534
Insistence on sameness	75 (56)	22 (51.2)	53 (58.2)	0.348
Restricted interests	69 (51.5)	18 (41.9)	51 (56)	0.106
Unusual interest in sensory aspects	98 (73.2)	35 (81.4)	63 (69.3)	0.990
Delayed motor milestones	44 (32.8)	21 (48.8)	23 (25.3)	**0.008**
Delayed self-help skills	82 (61.2)	24 (55.8)	58 (63.7)	0.295
CARS (mean ±SD)	43.1±5.2	42.2±4.4	43.6±5.5	0.170

DISCUSSION

Our study demonstrated that most signs of ASD emerged over the first 2 years of life. Children who were diagnosed at ≤24 months of age had poorer receptive language and motor skills than diagnosed after 24 months of age.

Studies investigating developmental profiles of ASD in children ≤24 months of age are limited (14). Malhi et al. (14) reported that clinical characteristics in the majority of children younger than 24 months with ASD were; no meaningful speech, no interest in children, lack of joint attention, unusual play, lack of pretend play, no index finger pointing, inability to follow verbal commands, motor stereotypies, and poor eye contact in a small sample (n=21), using a retrospective methodology. In our study, most common clinical characteristics of the children ≤24 months of age were similar to the study of Malhi et al. But unusual play (71.4% vs 88.3%), inability to follow verbal commands (81% vs 100%), and poor eye contact (66.7% vs 86%) were found more frequent in our study. This may be associated with larger sample size and including children with genetic and medical problems in our study.

There is a strong evidence that early identification and subsequently early intervention of ASD can improve cognitive, language and adaptive behavior and atypical behavior (15, 16) as well as other skills like joint attention (17, 18), communication (19), symbolic play (18), and imitation (20). In a review of 42 studies published from 1990 to 2012 showed that, the mean age at diagnosis decreased over time (21). Recent epidemiologic studies in United States and United Kingdom reported that the mean age of autism diagnosis remained at 4 to 5 years (22, 23). Similarly Zwaigenbaum et al. (24) found that the mean age of autism diagnosis was 38.2±8.7 months among Canadian preschool children. In Turkey, studies evaluating the age of diagnosis of autism are limited. Mukaddes et al reported the mean age of diagnosis as 2.39±0.75 years in 39 children (25). The average age at

diagnosis was 29.6±8.3 months in our sample. Our study group had a lower average age at diagnosis than other studies because we included the children under age 4, whereas other studies have included under age 8 (22).

In our sample, 8.2% of the children were diagnosed before 18 months of age and 23.9% of the children were diagnosed at 19-24 months of age. Landa (26) reported that approximately 50% of affected children could be diagnosed reliably by 14 months of age. Some clinicians want to see all the symptoms before delivering a lifetime diagnosis, but the wait and see approach might be detrimental by delaying access to early intervention services. Therefore, recommendation of American Academy of Pediatrics (AAP); a three-pronged approach consisting of routine, ongoing developmental surveillance, broad developmental screening at 9, 18, and 24/30 months, and universal ASD-specific screening at 18 and 24 months, is important for early diagnosis (27).

In our study, language delay was the most common first concerns reported by parents, in line with the literature (28, 29). In a Canadian study, better language and cognitive skills were determined as factors associated with late diagnosis of ASD (24). Similarly we found that poorer language skills such as inability to follow verbal commands were associated with early ASD diagnosis.

Daniels et al. (21) showed that factors like; greater symptom severity, higher socioeconomic status and greater parental concern were associated with earlier diagnosis. We found that higher maternal educational level and presence of parental concern were associated but symptom severity according to CARS was not associated with earlier diagnosis. It was reported that higher maternal educational level was associated with increased knowledge of child development in developing countries (30). Our findings supported that mothers with higher educational levels can recognize autism related symptoms earlier. However, only 1.5% of the parents named “autism” specifically as a concern. Our study showed that, parents were unwilling to express their suspicion of ASD clearly unless the history was detailed. In conjunction with the study of Richards et al. (29) our results emphasize the need for providers to ask and notice parents’ concerns during the diagnostic processes. It is important that professionals should take time to listen the parents and must be aware of their concerns related with ASD symptoms. On the other hand, parents attribute the child's condition to non-autism-specific behavioral difficulties, and beliefs such as, "he is stubborn", "he require more discipline", "he has difficult personality", or "he is spoiled" may lead to delayed diagnosis of ASD.

It is well known that ASD is about 4 times more common among boys than girls. In our study the boy to girl ratio was 4.1:1, in line with literature (2, 31). We found that gender was not associated with age of diagnosis in line with the literature (24).

There is a reasonable consensus that early motor difficulties may be an important early marker for ASD prior to formal diagnosis (32, 33). In a community-based cohort study from Australia, the prevalence of motor difficulties in ASD at the time of diagnosis was 35.4% (31). Similarly, motor delay was obtained 32.8% of the children with ASD at the time of diagnosis and it was more frequent in patients diagnosed at ≤24 months of age in our study. This may be due to the fact that a delay in motor domains can be more easily recognized than other developmental domains by parents and health care providers, and this leads to earlier referral of these children to comprehensive developmental evaluation.

In a meta-analytic review of 85 studies by Barger et al. (13), the overall prevalence of regression in children with ASD was estimated to be 32.1%, with an average onset at 21.4 months. In the current study, 32.8% of the children experienced regression; however, the median onset of regression time was earlier than previous studies according to parental reports. The children in our sample were younger than the children in the study of Barger et al. Therefore, earlier regression onset may be associated with “telescoping effect” which was described by Lord et al. (34) as parents providing information about older children tend to report later onset of symptom recognition. In conjunction with the study of Barger et al. (13), there was no significant difference between the regression rates in boys and girls.

Mamidala et al. (35) reported that parental consanguinity increased the risk for ASD with an odds ratio of 3.22. It increases the possibility of recessively inherited genetic diseases, congenital malformations, adverse perinatal outcomes including stillbirth, low birth weight, preterm delivery. Similarly with studies from Turkey (36, 37), consanguinity rate was 20.9%, in our study. These finding highlights the importance of developing national policies and strategies and educating people for consanguinity marriages.

It has been showed that children with ASD began to watch television earlier and had longer screen time compared with typically developing children (38). In a study from Turkey showed that, the frequency of exposure to mobile devices was 75.6% in young children and 20.6% of them were exposed before 12 months of age (39). Another study from Turkey reported that 82.4% of the children with language delay have daily screen time above 4 hours (40). We evaluated television screening time and, only 3.7% of children with ASD had screen time less than 1 hour, as recommended by AAP (41). It is known that in addition to child’s direct screen time, family screen time has negative impact on mother child reciprocal interaction (42). Thus, clinician should give advice to the families about the importance of limitation of the screening time as a part of anticipatory guidance in every visit.

Our study had some limitations. The most important

limitation was that ASD diagnosis was not based on structured tools such as the Autism Diagnostic Observation Shedule (ADOS) and the Autism Diagnostic Interview-Revised (ADI-R) due to the lack of Turkish validity and reliability. Retrospective design of our study was another limitation.

CONCLUSION

Reliable diagnoses of ASD can be challenging in very young children. Our study suggests that most signs of ASD emerged over the first 2 years. Children diagnosed ≤24 months of age have poorer receptive language and motor skills than children diagnosed later. Although motor delay was not included in DSM-V criteria, it can be an important predictor of ASD. Parents who are recognizing the warning signs of ASD may not express their concerns specifically as "autism". Therefore, it is important that pediatricians should be aware of the early signs of ASD and give time to listen the parents' concerns related with ASD signs.

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