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Research Article

Investigation of Demographic Characteristics and General Appearance of Individuals with Angelman Syndrome

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Abstract

Aim: Angelman syndrome (AS) is an autosomal dominant neurogenetic condition seen in 1 in 10000-22000 as a result of UBE3A gene dysfunction and microdeletion of the 15q11-13 region. The aim of this study is to determine the differences and similarities between individuals with AS by evaluating the demographic characteristics and general appearance of patients diagnosed with AS.
Material and Method: Age, gender, weight, height, BMI, weight, height and head circumference at birth, age of parents, type of birth, mother's gestation period, relationship status of mother and father, presence of genetic disease, dead or miscarried siblings number, parental smoking status, first appearance of clinical signs of the disease, epilepsy, scoliosis, sleep, nutrition, and speech problems, laughing attacks, tongue size, gait status, hair and eye color of 79 cases with genetic diagnosed AS case were evaluated.
Results: Of the individuals with AS who participated in the study, 40 (50.6%) were boys and 39 (49.4%) were girls. 43 of the patients (54.4%) were walking. The earliest walker among these patients started walking at the age of 3, and the latest walker started walking at the age of 13. 31 (40.5%) of our patients started walking between the ages of 3 and 4. When we asked the families when they noticed the first symptoms, all families realized that there were developmental problems before the child was 24 months old and consulted a physician. In fact, 70 of the families (88.6%) understood the problem before 12 months. When the time of onset of symptoms in boys and girls was compared, it was seen that the onset of symptoms was on average 2.82 months earlier in boys than in girls (p=0.004). The majority of cases with AS were thin, fair-skinned and blue-eyed individuals.
Conclusion: The parameters evaluated in our study revealed general and current data about the characteristics of individuals with AS.

Keywords: Angelman syndrome, general appearance, clinical features, UBE3A gene, microdeletion

INTRODUCTION

Angelman syndrome (AS) is an autosomal dominant neurogenetic condition seen in 1 in 10000-22000 as a result of UBE3A gene dysfunction and microdeletion of the 15q11-13 region. The syndrome was first described in 1965 by a British Pediatrician, Dr. Described by Harry Angelman. Although clinical findings vary from person to person, developmental delay, mental retardation, laughing attacks, epilepsy, autism spectrum disorder, hypotonia, bradykinesia, feeding and sleep disorders, hearing, speech and vision problems, and musculoskeletal system diseases are generally observed. The disease is also called 'Happy Puppet Syndrome' due to the presence of a constantly smiling facial expression in patients (1,2).

AS has different genetic mechanisms such as uniparental disomy, imprinting defect, UBE3A gene mutation and deletion. The most common of these is microdeletion, which occurs in 70-75% (3). Experimental studies have shown that UBE3A gene mutation causes synaptic and cellular changes in various parts of the brain (4).

In cases of AS, no abnormalities are observed before or during birth. The first symptoms of the disease occur at ages 6-12. It begins with developmental delay between months and months. Speech may be limited to a few words or not at all. During these periods, patients laugh excessively and have a constantly smiling facial expression (3). During these periods, families apply to the hospital thinking that there is a problem with the child.

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The definitive diagnosis is made as a result of genetic examination. It is similar to Rett Syndrome in terms of clinical findings. For this reason, genetic examination is very important (5). There are some important criteria in making a diagnosis. Of these, epilepsy and the presence of seizures starting before the age of three, abnormal electroencephalography (EEG) results and microcephaly are seen in 80% of individuals with AS. Craniofacial features such as flat occiput, wide mouth, widely spaced teeth, protruding tongue, feeding problems, sucking/ swallowing disorders, strabismus, hypopigmented skin according to family members, light hair and eye color, hyperactive lower extremity deep tendon reflexes, obesity (in older children; It is more common in those without 15q11.2-q13 deletion), clinical findings such as scoliosis and constipation are among the diagnostic criteria seen in individuals with AS. Metabolic, hematological and chemical laboratory findings are normal in the disease, and brain imaging findings are also normal, but mild cortical atrophy or dysmyelination may be observed (6).

There is no clear treatment for the disease. However, treatment methods have been developed to reduce or prevent existing problems. Anti-seizure medications are needed for epilepsy, physical therapy and rehabilitation are needed for musculoskeletal disorders and special education is needed for behavioral problems (7-9).

In line with this information, we aimed to determine the differences and similarities between individuals with AS by evaluating the demographic characteristics and general appearance of patients diagnosed with AS in our study.

MATERIAL AND METHOD

Study of data was collected by interviewing the families of individuals with AS in different cities of Türkiye in the Angelman Türkiye Community. First of all, consent was obtained from the families, who agreed to share their children's information completely. Then, data were collected by interviewing 82 families. However, 3 children with AS with missing information were excluded from the study. The cases were patients who went to the hospital regularly and did not miss their check-ups since their diagnosis. Therefore, all the data we wanted to access was available in the patients' files.

The case's age, gender, weight, height, body mass index (BMI), weight, height and head circumference at birth, age of parents, type of birth, mother's gestation period, relationship status of mother and father, presence of genetic disease, number of siblings, dead or miscarried sibling, information about the number of children, their parents' smoking status, age at first appearance of clinical signs of the disease, epilepsy, scoliosis, sleep, nutrition, speech problems, laughing attacks, tongue size, and walking status were evaluated. At the same time, hair and eye color were evaluated regarding the child's physical appearance. It was also questioned at what age the patient was diagnosed and whether he received special educational support.

Statistical Analysis

Data were evaluated with IBM SPSS V.29. Descriptive statistics were given as mean and standard deviation for normally distributed data, median, quartiles and minimum-maximum values for non-normally distributed data. Categorical data were summarized with numbers and percentages. Independent samples t test was used to determine the relationship between two averages. In statistical analysis, the significance level was considered as $p<0.05$.

RESULTS

Of the individuals with AS who participated in the study, 40 (50.6%) were boys and 39 (49.4%) were girls. The average age of the participants was 11.82. When the presence of a genetic disease in their relatives was questioned, it was seen that only 8 (10.1%) had a genetic disease in their first or second degree relatives, while the remaining 64 (89.9%) patients did not have any genetic disease in their relatives.

According to the frequency analysis 51 (64.6%) of the cases were born by cesarean section and 28 (35.4%) were born by vaginal birth. Most patients had a normal gestational age (Table 1).

The birth weights of the patients were evaluated. There were 13 (16.5%) cases weighing less than 2500 grams. There were 2 (2.6%) cases born weighing 4000 grams and above. The weight of 54 of the cases (80.9%) was between 2500 and 4000 grams. The maximum birth weight of the patients was 4600 grams and the minimum value was 1300 grams. The average birth weight was calculated as 2979,43 grams. Considering their height at birth, 12 (11.4%) cases were born with a height of 45 cm or less. The maximum birth height of the patients was 61 cm and the minimum value was 43 cm. The average birth height was calculated as 50.05 cm. When the head circumference at birth was evaluated, the head circumference of 59 (74.7%) of the cases was 35 cm or less.

When the ages of the mother and father were evaluated at the time of birth, there were 15 (19%) mothers who were 35 and over, while the majority of mothers' ages were between 20-34 years. When the ages of the fathers were evaluated, there were 56 (70.9%) fathers aged 35 and under, while there were 23 (29.1%) fathers over the age of 35. When the smoking status of the mother and father was questioned, 14 of the mothers (17.7%) and 40 of the fathers (50.6%) were smokers. When the kinship status between the patients' mothers and fathers was evaluated, 5 (6.3%) were close relatives and 10 (12.7%) were distant relatives. There was no consanguineous relationship between the parents of 64 (81%) patients. When the number of miscarriages experienced by the patient's mothers before was evaluated, 20 of the mothers (25.3%) had experienced 1 miscarriage and 3 of them (3.8%) had a history of 2 miscarriages. 56 of the mothers (70.9%) had no history of miscarriage.

All patients were diagnosed with AS in genetic analysis. When we asked the families when they noticed the first symptoms, all families realized that the child had developmental problems before the child was 24 months old and consulted a physician. According to the frequency analysis, 70 of the families (88.6%) had understood the problem within 12 months (Table 2). When the time of onset of symptoms in boys and girls was compared with Independent samples t test, it was observed that there was a significant difference between the age at which the first symptoms were noticed in male and female patients. It was seen that the onset of symptoms was on average earlier in boys than in girls (p=0.004).

It took time for the family to realize the situation, consult a doctor and make a clear diagnosis. According to the frequency analysis when the age at diagnosis of the patients was evaluated, the earliest diagnosed patient was 1 year old, while the latest diagnosed patient was 14 years old (Table 3). There was no significant difference in age at diagnosis between boys and girls.

While 66 (83.5%) of the patients were also diagnosed with epilepsy, 64 of them frequently had seizures. There was no history of seizures or epilepsy in 13 of the patients (16.5%). Laughing attacks, feeding and sleeping problems, and hyperactivity status of the patients are shown in the table (Table 4).

Only 3 of the patients (3.8%) could speak. Others had a limited number of word outputs. While 44 of them could make monosyllabic sounds, the others (37) could make an average of 5 to 10 words. When male and female patients were compared, it was observed that male patients had an average of 5.23 words and female patients had 1.77 words on average, but there was no statistically significant difference between them (p=0.136). 43 of the patients (54.4%) were walking, and the earliest among these patients started walking at the age of 3, while the latest walked at the age of 13. 31 (40.5%) of our patients started walking between the ages of 3 and 4. 27 of the patients (34.2%) had scoliosis. We also found that 20 (25.3%) of the patients had larger than normal tongue sizes and had drooling problems. When the hair and eye color of the patients were evaluated, we saw that there were more patients with brunette and blue eyes (Figure 1, Figure 2).

As a result of the BMI scores calculated by evaluating the weight and height of the patients, the average BMI value of the patients was calculated as 19.21. 40 (50.6%) of the patients were underweight, 24 (30.4%) were normal, 11 (13.9%) were overweight, 2 (2.5%) were 1st degree obese, 2 were (2.5%) was found to be 2nd degree obese.

Table 1. Pregnancy period; Pregnancy periods and distribution are given in the frequency analysis table

Pregnancy week	Frequency	Percent (%)
41	6	7.6
40	22	27.8
39	10	12.7
38	19	24.1
37	7	8.9
36	4	5.1
35	3	3.8
34	4	5.1
33	1	1.3
31	1	1.3
30	1	1.3
28	1	1.3

Table 2. Months when the family first noticed the problems and consulted a physician

The month	Frequency	Percent %
1	16	20.3
2	2	2.5
3	3	3.8
4	5	6.3
5	8	10.1
6	15	19.0
7	5	6.3
8	5	6.3
9	4	5.1
10	4	5.1
11	3	3.8
13	1	1.3
14	3	3.8
15	1	1.3
18	2	2.5
20	1	1.3
24	1	1.3
Total	79	100.0

Table 3. Age at diagnosis

Age	Frequency	Percent %
1	27	34.2
2	22	27.8
3	1	1.3
3	17	21.5
4	7	8.9
5	1	1.3
6	2	2.5
12	1	1.3
14	1	1.3
Total	79	100.0

Table 4. Laughing attacks, feeding and sleeping problems, presence of hyperactivity in patients

	Feeding problems		Sleep problems		Laughing attack		Hyperactivity	
	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent
Yes	51	64.6	65	82.3	52	65.8	63	79.7
No	28	35.4	14	17.7	27	34.2	16	20.3

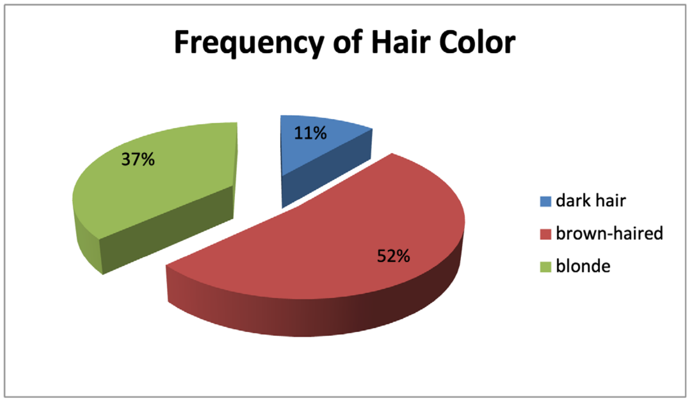

Figure 1. Hair color of patients

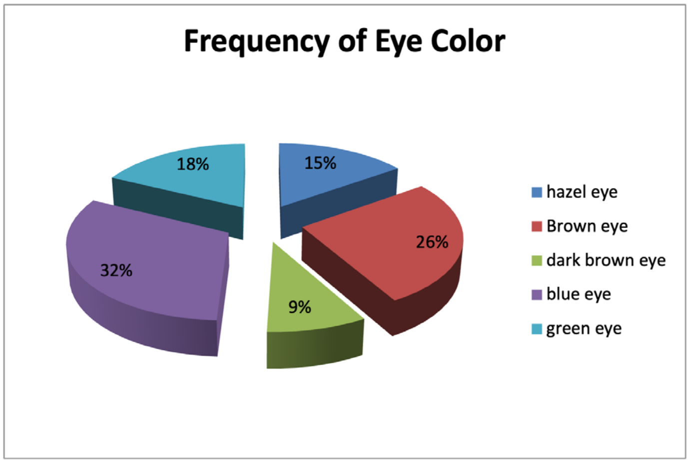

Figure 2. Eye color of patients

DISCUSSION

In this study, demographic information and general appearance of 79 patients diagnosed with AS were evaluated. At the same time, the differences and similarities between individuals with AS are emphasized. The fact that there are few studies on this subject or that the studies are mostly in the form of case reports adds value to our article.

According to a study conducted in 2022, the first studies on AS started in 1965. Genetic research accelerated in 1993. To date, 2663 studies on this subject have been added to the literature (10).

In a cohort study conducted with a literature review, 48 male and 47 female cases were included and the average age was reported as 31.6 years (11). In a study conducted in China where 577 cases of individuals with AS were evaluated, the average age was calculated as 6.34±2.94 years. No significant difference was found between age and gender (12). In a study where 100 patients diagnosed with AS, 50 girls and 50 boys, were evaluated between 2010 and 2017, the average age was 5.7 years (13). In our study, the ratio of girls to boys was similar and the average age was 11.82. Although the average age in our study is consistent with some studies in the literature, it is expected to differ from some studies and vary depending on country and time.

The genetic basis of the disease suggests that genetic diseases in the family should be questioned. In a study, only 17 of 577 patients were found to have a genetic disease in their family (12). In our study, genetic disease was found in the first and second degree relatives of only 8 of our patients. This may be explained by the fact that the disease is rare and less likely to come from the mother or father.

An 11-year-old case reported in 2021 weighed 3600 grams. It was observed that the baby was born normally and there were no problems in the prenatal period (14). Akça et al examined 5 cases in a study. One of these cases had a diagnosis of Prader Willi syndrome. All cases were born normal and on time (15). In another study, the average birth weight of 80 cases whose birth weights were reached was reported as 3.117gr (11). In a study evaluating a 7.5-year-old case, it was stated that the patient's weight, height and head circumference measurements at the time of birth were within normal values (16). 92% of the 87 cases for which information was available during pregnancy were term babies. Of the cases we evaluated, 80.9% were of normal weight and 88.6% were of normal height at the time of birth. The majority of cases diagnosed with AS are no different from normal babies at the time of birth. It is a disease that is noticed by delayed development in the first few years. For this reason, our data were found to be compatible with the literature.

In our study, the gestational ages of the mothers were concentrated between 20 and 34. There were 19% mothers over the age of 35. In another study, the gestational ages of the mothers ranged between 26 and 39 (11). The increase in the age of marriage also results in an increase in the gestational age. In this case, advancing age brings with it risky pregnancies. In our study, when the mothers were questioned about their miscarriage pregnancies, it was seen that 29.1% had a history of 1 or more miscarriages. In one case reported by Knezevic et al., the mother had a previous history of miscarriage (9).

The diagnosis of the disease, which begins with developmental delay, is confirmed by genetic screening. In this case, the family, realizing that the development has passed, consults a physician. Early recognition by the family enables the diagnosis to be made earlier. In our cases, families noticed developmental problems before the child was 24 months old and consulted a physician. In a study conducted in 2021 with people who cared for individuals with AS for a long time, it was seen that the first ones to notice the symptoms were mostly caregivers and their complaints were compatible with the physician's diagnosis (8). In one reported case, the first symptoms were noticed by the family at the 6th month and the diagnosis was made at the age of (2,9). In another case, the patient's first symptoms were noticed by the family when she was 13 months old, and the age of full diagnosis was 7.5 years old (16). In a study evaluating 95 cases, it was stated that the first symptoms of 82% of the cases began to appear in the first few months and the average age of diagnosis was 6.8 years (11). The average age at diagnosis of 219 cases, aged between 0-18, was 6 months (17). With the advancement of technology, increased doctor's checks and increased awareness of families, diseases with a genetic basis are diagnosed at an earlier age.

Epilepsy is a very common clinical condition in patients with AS. In a study, 55% of the patients had epilepsy, while in another study, 82% of the patients were diagnosed with epilepsy (12,13). In a study examining 265 cases aged between 0 and 18, 46 cases did not experience seizures. Among 219 cases, 54% were diagnosed with AS before their first seizure (17). In another reported case, it was stated that there was no epileptic seizure and no diagnosis of epilepsy was made (9). In our study, most of the patients (83.5%) were diagnosed with epilepsy. The diagnosis of epilepsy, which is seen in most cases of AS, may not be seen in some cases.

Feeding and sleeping problems, laughing attacks, hyperactivity and scoliosis are among the common findings in patients with AS. In a study published in 1995, the clinical findings seen in all AS individuals were classified as developmental delay, speech disorder, balance and coordination problems, behavioral disorders, laughing attacks, stereotypical movements, and short attention span (18). When the studies were examined, cases where these findings were observed frequently were found (9,11). In a study evaluating 94 cases, 50 of the patients had scoliosis (11). In another study, 17.5% of cases had scoliosis (12). Scoliosis developed at different levels and degrees in 34.2% of our cases.

In a study 100 patients were evaluated. In the study, it was reported that all patients had feeding problems and 13 patients even required tube feeding before or at that time (19). Our cases had similar nutritional problems.

Sleep problems were present in 81 of 92 cases whose information was obtained in the studies (11). In another study, the rate of people with sleep problems was reported to be 91% (13). In a systematic review in which 14 studies were analyzed, data from 133 female and 133 male patients were evaluated. The sleep problems of the patients were investigated and it was stated that they had many problems with falling asleep, wakefulness, and sleep duration (20). Consistent with the literature, there were 82.3% of patients with sleep problems in our study.

Developmental delay in patients with AS causes them to walk and talk later. In our cases, 54.4% of the patients were walking, and the earliest among these patients started walking at the age of 3, while the latest walked at the age of 13. 40.5% of our patients started walking between the ages of 3 and 4. In a study, 65% of 92 cases were walking independently. There were 13% cases who walked with support and 22% who could not walk at all (11). In studies, the average walking age of patients diagnosed with AS was found to be 2.6 years, 5.125 years, 2 years, 3 years, 2.9 years (21-26). The diagnosis of the disease, the patient's age and development, and the age at which physical therapy begins directly affect the patient's walking status. The difference in findings in the studies may be due to these situations. For this reason, every child diagnosed with AS should undergo a detailed physical examination and, if necessary, physical therapy and rehabilitation should begin at the earliest. When the speech status of the patients was evaluated, in one study, 20 out of 92 cases could not speak at all. But others could say even a few words (11). In another study, there was no word output in 80.24% of the cases. Only 0.87% could speak short sentences (12). Similarly, in our study, the majority of patients could not speak, while others could say monosyllabic or simple words. The frequency of speech problems seen in individuals with AS indicates that speech-language therapy should be started after diagnosis.

Studies have shown that hair, skin and eye color may be lighter in individuals with AS (27). When the general characteristics of individuals with AS were examined, it was reported that 88% had blue eyes and 65% had blonde hair (14). In the study of Lossie et al., the rate of patients with light skin and light hair was found to be 20%, while in the study of Payatos et al., this rate was reported as 33% (21,22). Another study reported that 77.30% of cases had light skin color (12). Unlike the literature, we evaluated the hair and eye colors of the patients. Our data similarly showed that patients had lighter skin. The majority of our patients were brown-haired (52%) and blonde (37%), and their eye colors were blue (32%).

The patients' weight and height were recorded and their BMI was calculated. According to these calculations, the majority of our patients (50.6%) were found to be underweight. In studies, the weights of patients were evaluated and a rate of 33.3% to 20% of obese cases was found (21-26). The average weight of 78 cases is 68 kg. There were 45 cases with normal BMI, 4 underweight cases, 20 overweight cases and 9 obese cases (11).

In this syndrome, maternal pregnancies are generally normal and birth weights are no different from normal. However, they may be underweight due to subsequent nutritional problems (28). In our study, the large number of cases that were young and had nutritional problems caused their weights to be low.

Today, there is still no treatment that provides repair of the chromosomal defect and restoration of the mutant gene. Ultimately, treatment focuses on the patients' neurological and physical problems. For this reason, treatment is symptomatic. Training and rehabilitation provided to increase the comfort of life of patients are the most important forms of treatment and a multidisciplinary approach is required in these treatments (15). All patients in our study received physical therapy, age-appropriate speech therapy and special education support. Studies have shown that alternative therapies such as massage and aromatherapy help increase concentration and reduce hyperactivity (15).

CONCLUSION

In our study, the demographic information and general characteristics of 79 individuals with AS were evaluated and the similarities and differences between them were noted. All cases evaluated were individuals who did not experience any problems during and at the time of birth. Additionally, most of our patients were fair-skinned and blue-eyed children. The diagnosis process usually started when the family consulted a physician due to developmental delay. For this reason, it is very important for families to be aware, to take into account the developmental delays seen in infancy and not to neglect the necessary medical check-ups.

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