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ETIOLOGY, DIAGNOSIS, AND MANAGEMENT OF CHILDHOOD MICROCEPHALY: A SINGLE-CENTER RETROSPECTIVE STUDY

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ABSTRACT

Background: Microcephaly is a condition that causes a reduction in brain volume as well as cognitive and motor impairments. It can be seen alone or in conjunction with a variety of genetic disorders and environmental factors. Microcephaly is still a poorly defined condition, identifying the etiological causes is critical for providing genetic counseling, and preventing potential consequences.
Objective: The aim of this study was to assess the etiology, diagnosis, and management of the childhood microcephaly.
Methods: We conducted a retrospective analysis on 50 children with microcephaly (25 males, 25 females) who presented to University of Health Sciences, Ankara Keçiören Training and Research Hospital between 2017-2021.The demographic features of the patients, neuroimaging, clinical and laboratory findings were examined.
Results: The etiology of microcephaly was documented in 76% of all patients. Genetic causes were identified in 16 % of the patients; including Aicardi Goutieres Syndrome,Williams Syndrome , Wolfram Syndrome, Rett Syndrome and Asparagine Synthetase Deficiency. Syndactyly, scoliosis, Poland syndrome, dysmorphic face, alopecia, auricular ear deformities, hearing loss, strabismus, nystagmus, hydronephrosis, single umbilical artery, and cardiac septal defect were detected systemic malformations associated with microcephaly. In sixty percent of the patients, a neuroimaging was performed; results were abnormal in 24% of the patients. The mean follow-up period of the patients was 1.88± 0.6 years. Cognitive impairment was associated with microcephaly in 38% of the cases, and epilepsy in 20%. Of those 28% of the children required special education. One patient was operated by neurosurgeon due to craniosynostosis.
Conclusion: Microcephaly is still a poorly defined condition, identifying the etiological causes is critical for providing genetic counseling, and preventing potential consequences.

Keywords: Microcephaly, etiology, childhood, genetic

Introduction

Microcephaly is described as having an occipitofrontal head circumference (OFC) that is less than the third centile or more than two standard deviations (SD) below the mean for sex, age, and ethnicity.[1-3] Its incidence is varies from 1.3 to 150 per 100,000 births.[4] Microcephaly is associated with a decrease in brain volume as well as intellectual and/or motor difficulties. The etiology of microcephaly is heterogeneous, ranging from inherited causes to environmental variables that may change developmental processes that control the brain size. Microcephaly can be present at birth (primary microcephaly) or occur after birth (secondary/ acquired/microcephaly). Questioning the birth head circumference and subsequent OFC measurements in the history are important in terms of distinguishing whether microcephaly is primary or secondary and guiding clinicians in differential diagnosis.

Microcephaly is still a poorly defined condition, identifying the etiological causes is critical for providing genetic counseling, and preventing potential consequences. The aim of this study was to assess the etiology, diagnosis, and management of the childhood microcephaly.

Methods

Patients with a diagnosis microcephaly were drawn from all children who came to the Departments of Pediatric Neurology at Ankara Keçiören Training and Research Hospital between 2017 and 2021, respectively. Microcephaly was defined as an OFC that was lower than the third centile for gender and age. It was further classified as primary if it appeared at birth or secondary if it appeared later in life. The following study variables were collected from hospital records: demographic features, age of microcephaly diagnosis, prenatal/ natal history,

developmental milestones, family history, accompanying clinical features, head circumference measurements, systemic and neurological examination findings, laboratory, genetic, and neuroimaging findings were recorded. Etiological investigations including Denver II Developmental Screening Test (DDST), TORCH scan results, metabolic tests, electroencephalography (EEG), head x-ray, cranial magnetic resonance imaging, ultrasonography and computerized brain tomography (CT) and genetic analysis results were recorded if available.

IBM SPSS 25 program was used for statistical data and graphics. Data were analyzed using descriptive statistics and the results presented in absolute frequencies, percentages, means and standard deviations.

Approval was obtained from the Local Ethics Committee (24.08.2021 -No: 2012-KAEK-15/2346) for this retrospective study.

Results

A total of 50 (25 male and 25 female) patients with microcephaly were included. The mean age of patients at first admission was 16.60±2.46 months (range 1- 75 months). Microcephaly was proportionate in 18% (n=9) of the patients. Seventeen patients (34%) were defined as primary microcephaly and 33(66%) were defined as secondary microcephaly. The mean maternal age at birth was 26±4.2 years (range 15- 37 years). The mean gestational age of patients were 37.6±2.8 weeks (range 26-42 weeks) and the mean birth weight was 2842± 583gr (range 1260-3800gr) (Table 1).

Forty-three (86%) of the patients were born at term and seven (14%) were born prematurely. Parental consanguinity was present in 22% (n=11) of the patients and small head circumference was detected in 8% (n=4) of the parents. A small head circumference was detected in 8% (n= 4) of the patients on prenatal ultrasonography.

The etiology of microcephaly was documented in 76% (n=38) of the patients (Table 2). A history of neonatal hyperbilirubinemia requiring phototherapy was detected 12% (n=6), prematurity 14% (n=7), invasive mechanical ventilation 12% (n=6), birth asphyxia 6% (n=3), and intrauterine Cytomegalovirus (CMV) infection 4% (n=2). Metabolic work up revealed abnormality of urine/blood aminoacids in 6% (n=3) of all patients. Laboratory investigations showed vitamin D deficiency in 2% (n=1) and hypothyroidism in 2% (n=1) respectively. One patient had fetal alcohol syndrome.

A genetic etiology was detected in 16% (n=8), including Aicardi Goutieres Syndrome (n=1), Williams Syndrome (7q11 del) (n=1), familial hypercholesterolemia type 3 (3.10q11.22 large deletion, GPRIN2/NPYR4R gene involvement (n=1), DIDMOAD (Wolfram) Syndrome(n=1), Rett Syndrome(NM_004992.4 c.455C>G (p.P152R) (p.Pro 152Arg) heterozygous mutation in MECP2 gene (n=2), and Asparagine Synthetase Deficiency (n=2). Other systemic malformations and abnormalities associated with microcephaly including: syndactyly (4%), scoliosis (2%), Poland syndrome (2%), dysmorphic face (4%), alopecia (2%), auricular ear deformities (4%), hearing loss (2%), strabismus (6%), nystagmus (2%), hydronephrosis (2%), single umbilical artery (2%), and cardiac septal defect (6%) were also detected.

In 60 percent of the patients (n=30), a neuroimaging was performed, including cranial magnetic resonance imaging (38%), cerebral ultrasonography (12%), computerized tomography (12%) and cranial X-RAY (8%). The mean age at cranial magnetic resonance imaging (c MRI) was 24 months, and transcranial ultrasound was 2 months. Neuroimaging results were abnormal in 24% (n=12) of the patients. Apart from microcephaly, the most common neuroimaging abnormalities were white matter anomalies (41.6%), corpus callosum agenesis/digenesis (25%), gyration abnormalities (16.7%) and ventricular abnormalities (16.7%) (Figure1).

The mean follow-up period of the patients was 1.88± 0.6 years (1-3 years). Developmental delay was detected in 38% (n=19) of patients on Denver II Developmental Screening Test. Of those 28% (n=14) of the children required special education. Cerebral palsy was found in 10% (n=5) of the patients. Epilepsy was diagnosed in 20% (n=10) of the patients and they all were using antiepileptic drugs. One patient was operated by neurosurgeon due to craniosynostosis.

Discussion

Genetic and environmental factors that influence the development of cerebral size prenatally or postnatal regulate the basic processes of cerebral growth and proliferation.[3,4] Any condition that affects cerebral integrity from early stages of development to the period of rapid postnatal growth can cause microcephaly.[5] Patients with primary microcephaly were 34% and secondary microcephaly were 66% in our study.

In the literature, hypoxic–ischemic encephalopathy (HIE) is the most common cause of acquired microcephaly.[6] The presence of white matter lesions, as well as significant basal ganglia and thalamic lesions, is connected to secondary microcephaly in HIE neonates. Infants with HİE and inadequate head growth but normal development at one year of age should be regularly monitored. At that age focus mostly on motor items, but cognitive, perceptual, or subtle neurological indications may emerge later in childhood.[6] Prematurity was found in 14% of our patients, invasive mechanical ventilation in 12%, and asphyxia in 6% of our patients. These factors may have contributed to HIE development and susceptibility to microcephaly.

Prenatal alcohol exposure (PAE) is a leading cause of avoidable birth abnormalities and developmental disorders in children.[7] Toxic byproducts of alcohol metabolism build up in the body, affecting cell development, division, and survival. Fetal alcohol syndrome includes three characteristic facial anomalies (short palpebral fissures, thin upper lip, smooth philtrum), height and/or weight <10th percentile (prenatal and/or postnatal), structural CNS abnormalities, neurobehavioral and cognitive impairment. Malformations can occur depending on the time and severity of PAE.[7] Alcohol may cause changes in gene expression in crucial brain regions.[8]

Table1. Distribution of microcephaly cases according to mother's age, gestational age at delivery and birth weight

	Total cases(n=50)	Minimum	Maximum	Mean	Std. Deviation
Mother's age(years)	50	15	37	26	4.2
Gestational age at delivery(weeks)	50	26	42	37.6	2.8
Birth weight(gr)	50	1260	3800	2842	583

Table 2. Demographic, clinical and laboratory features of microcephaly cases

	Total Cases (n=50)	Frequency (**%**)
Age (months) (mean±std)	16.60±2.46 months (min 1-max 75)	
Gender		
Female	25	50
Male	25	50
Consanguinity	11	22
Small head circumference in one of parents	4	8
Prematurity (Gestational age<37 week)	7	14
Microcephaly Etiology		
Primary	17	34
Secondary	33	66
Proportionate microcephaly	9	18
Etiologic diseases		
Aicardi Goutieres Syndrome	1	2
Williams Syndrome (7q11 del)	1	2
Familial hypercholesterolemia type 3 (3.10q11.22 large deletion, GPRIN2/NPYR4R gene involvement)	1	2
DIDMOAD (Wolfram) Syndrome	1	2
Rett Syndrome	2	4
Asparagine Synthetase Deficiency	2	4
Neonatal hyperbilirubinemia*	6	12
Prematurity*	7	14
Invasive mechanical ventilation*	6	12
Asphyxia	3	6
Congenital *Cytomegalovirus* infection	2	4
Fetal alcohol syndrome	1	2
Abnormal urine/blood amino acids	3	6
Vitamin D deficiency*	1	2
Hypothyroidism*	1	2
Abnormal c MRI**	12	24
Neurodevelopmental delay	19	38
Special education	14	28
Epilepsy	10	20
Follow-up period (mean±std)	1.88± 0.6 years (1-3 years)	

*Possible etiologic factors **Cranial magnetic resonance imaging

One of our patients showed signs of fetal alcohol syndrome. She had a typical dysmorphic face with smooth philtrum, thin upper lip, small palpebral fissures, as well as cerebral palsy, growth retardation, hearing loss, and eyesight issues.

The c MRI revealed agenesis of the corpus callosum and holoprosencephaly. This patient was diagnosed with neurodevelopmental delay and epilepsy.

Intrauterine infections associated microcephaly was caused by three of the original "TORCH" agents (Toxoplasma Gondi, Rubella Virus, and Cytomegalovirus) and ZICA Virus.[9] These infections cause significant loss of neural tissue during the early development of the fetal central nervous system (CNS) due to their neurotropism.[10,11] Microcephaly is frequently linked with other symptoms such as intrauterine growth retardation (IUGR), neurodevelopmental abnormalities, ophthalmologic abnormalities, and sensor neural hearing loss. Congenital cytomegalovirus (CMV) infection was detected two of our patients. These patients exhibited intellectual disabilities as well as delays in their neurodevelopment. One of them had epileptic seizures that began when he was 11 months old, and he was taking two different antiepileptic medications.

In the literature; genetic etiologies are shown to be responsible in 15.5% to 53.3% of children with microcephaly.[12,13] A wide variety and different number of chromosomal disorders may cause microcephaly such as Rett syndrome, Down syndrome, Cri du chat syndrome, Seckel syndrome, Rubinstein-Taybi syndrome, trisomy 13, trisomy 18, Smith-Lemli-Opitz syndrome, and Cornelia de Lange syndrome, autosomal recessive primary microcephaly. [13,14] The etiology was genetic in 16% in our cohort. Aicardi Goutieres Syndrome (AGS), Williams Syndrome (7q11 Del), Familial hypercholesterolemia type 3 (10q11.22 large deletion, GPRIN2/NPYR4R gene involvement), DIDMOAD (Wolfram) Syndrome and Rett Syndrome were detected genetic causes.

5 gene mutations can be responsible for 90% of the cases.[15] Our patient with AGS had corpus callosum agenesis and brain stem atrophy, hypoplasia in c MRI and mental-motor retardation. Williams's Syndrome (WS) is an uncommon congenital condition marked by unusual facial traits, congenital cardiac problems, and behavioral symptoms such as mental retardation. In terms of cranial morphology, microcephaly was very common.[16]

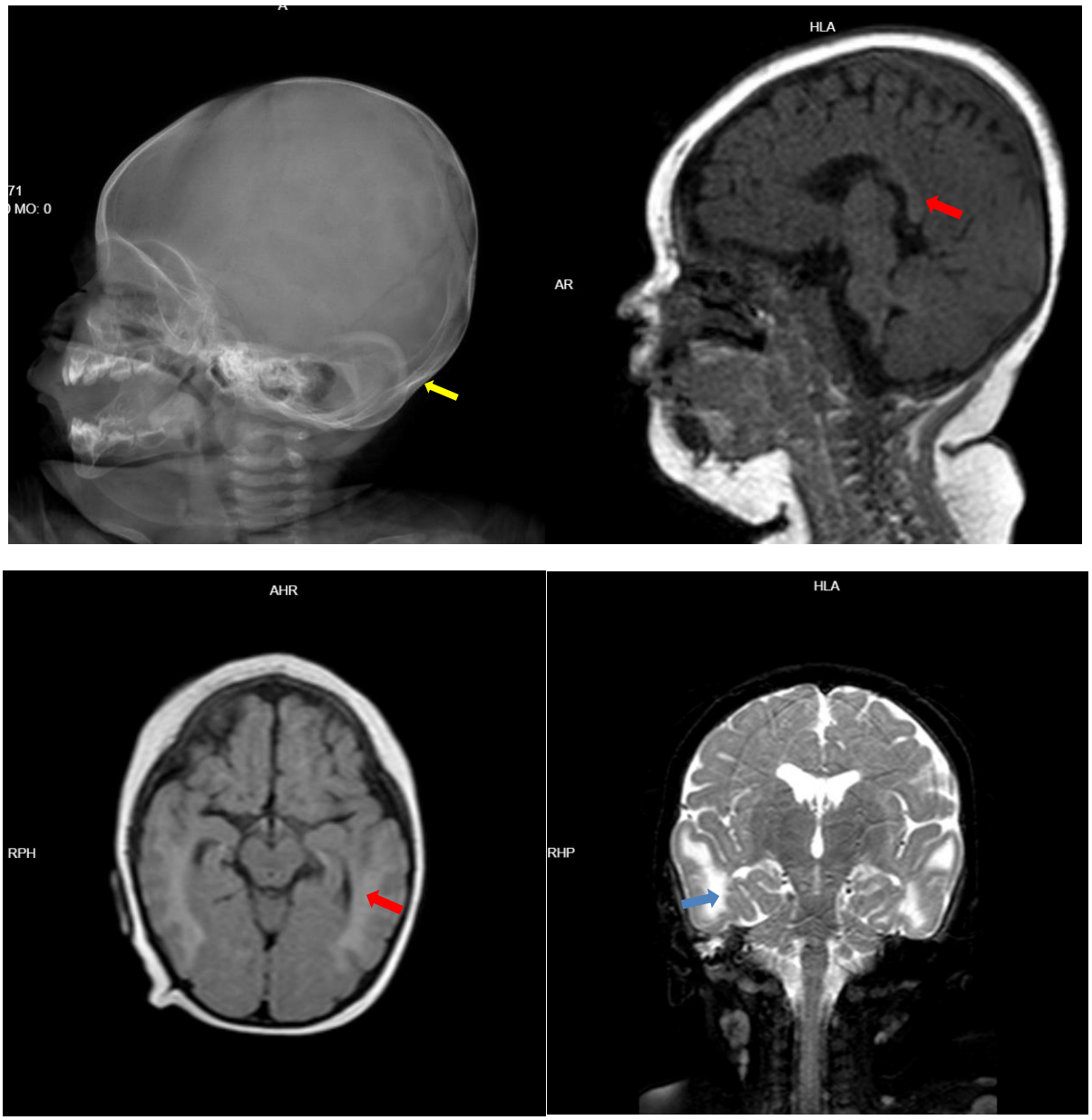

Figure1. Cranial imaging of a microcephaly patient
*Microcephaly and trigonocephaly can be seen on cranial X-ray (yellow arrow). There is hypoplasia/atrophy of the corpus callosum and brain stem (red arrow), as well as a detectable increase in white matter signal (blue arrow) on c MRI.

Our WS patient had a history of prematurity, a typical face, patent foramen oval and pulmonary stenosis. He also had epilepsy and mental retardation. Patients with 10q11.22 deletions rare diseases revealed with variable clinical features.[17] Developmental delay, intellectual disability, epilepsy, autism spectrum disorders, corpus callosum abnormalities, ataxia can be detected. In literature microcephaly is found 19% of these patients.[17] Our patient had microcephaly, familial hypercholesterolemia and intellectual disability. 10q11.22 large deletion, GPRIN2/NPYR4R gene involvement was found in genetic analysis. DIDMOAD (Wolfram) syndrome is a rare autosomal recessive condition that was initially identified as a combination of early-onset diabetes, progressive optic nerve atrophy, diabetes insipidus, and sensor neural hearing loss. AGS is an autosomal recessive genetic disorder, clinically characterized by microcephaly, cerebral atrophy, white matter abnormalities, mental-motor retardation, and intracranial calcification especially at basal ganglia. AGS1-Furthermore, Wolfram syndrome has been linked to a number of congenital malformations such as microcephaly.[18] Our patient had diabetes, optic nerve atrophy, diabetes insipidus, and hearing loss, also microcephaly and mental retardation. Rett syndrome (RTT) is an X-linked neurodevelopmental disorder due to mutations in the MECP2 gene. It typically becomes apparent after 6–18 months of age in females. Symptoms include impairments in language, coordination, walking difficulty, slow growth, a smaller head size and seizures.[19] Both of our patients had a normal head size at birth after displayed autistic-like symptoms such as loss of social interaction and communication. Slowed head growth was noticed during this stage. One of them had epileptic seizures. The other had NM_004992.4 c.455C>G (p.P152R) (p.Pro 152Arg) heterozygote mutation in MECP 2 gene. This patient had stereotypical head-shaking

movements, speech delay, axial and peripheral hypotony and broad-based walking. Therefor RTT is an important disorder to be considered in girls who have acquired microcephaly. Asparagine Synthetize Deficiency (ASNSD) is an uncommon autosomal recessive inborn metabolic mistake caused by a mutation in the ASNS gene, which codes for asparagine synthetize.[20] Deficiency of asparagine in brain or accumulation of aspartate/glutamate results in the neurological manifestations. It has a severe neurological phenotype that includes developmental delay, congenital microcephaly, spasticity, and refractory seizures.[21] Our two patients were cousins and they were diagnosed at the age of three. They both suffered microcephaly, growth retardation, mental retardation, cerebral palsy, stereotypical movements, and epilepsy. The follow-up of these patients, previously reported in the literature, continues in our hospital.[22]

A frequency of 1-5 percent has been recorded in the case of metabolic problems as a cause of microcephaly.[1,2] Secondary microcephaly is generally linked to increased neuronal death and metabolic disorders such serine insufficiency and thiamine pyrophosphate transporter failure.[1] Abnormal urine/blood amino acids were positive in 6% (n=3) of all patients. Alanine, lysine, ornithine, phenylalanine, taurine elevation was detected in one of our patient; he had psychomotor retardation and epilepsy. The other two patients had elevated hydroxylysin and homocysteine levels, but no significant neurological issues.

In patients with microcephaly, ophthalmological problems, facial dysmorphism, oropharyngeal anomalies, and heart, kidney, urinary tract, skeletal system, and gastrointestinal tract anomalies are all common systemic malformations associated with microcephaly.[2] Similar to literature, our patients had syndactyly, scoliosis, Poland syndrome, face dimorphism, auricular ear abnormalities, hearing loss, strabismus, nystagmus, hydronephrosis, single umbilical artery, and cardiac septal defects.

Cranial imaging is not mandatory in every patient. However, in the presence of primary microcephaly, severe intellectual disability, early-onset epilepsy, motor findings or a family history such, it is necessary to have information about cerebral formation by performing cranial imaging. In literature 61% of microcephaly patients have abnormal neuroimaging findings; this rate was found to be 75-80% in severe microcephaly.[23,24] Cranial magnetic resonance imaging allows us to detect structural brain malformations and migration anomalies. White matter anomalies, corpus callosum anomalies, gyration abnormalities were the most seen abnormal findings in addition to microcephaly in our study.

Children with microcephaly have a low IQ and also learning disabilities were documented.[24] Age, gender, socioeconomic status, family head circumference measurements, and prenatal nutrition indicators have all been discovered to be significant. Early special education commencement in cases of microcephaly can improve the prognosis.[25,26] The Denver Developmental Screening Test II was used to measure our individuals' psychomotor development, which found that 38 percent of them had psychomotor impairment. Furthermore, 28% of our cases required special schooling. Total prevalence of epilepsy has been reported to be 40.9%.[27,28] Epilepsy was diagnosed in 20% of our patients and they all were using antiepileptic drugs. Epilepsy and mental impairment are both associated with microcephaly. As a result, patients of microcephaly should be constantly monitored in terms of epilepsy and mental impairment, and counseling provided.

Conclusion

Microcephaly is a common symptom of a wide range of uncommon disorders. A metabolic and genetic study is required if there is a family history of consanguinity or mental impairment. If there are aberrant neurological examination findings and simultaneous multisystem involvement, neuroimaging is indicated. A precise diagnosis is necessary for patient and family counseling on the clinical course, potential consequences, optimal medical assistance, and recurrence risk and critical for development of neuro protective medicines.

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Conflict of Interest

No funding to declare. There are no conflicts of interest in connection with this paper.

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