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CLINICAL-NEUROLOGICAL AND INTELLECTUAL CHARACTERISTICS OF MICROCEPHALY OF VARIOUS ETIOLOGIES

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BACKGROUND

According to contemporary data, the prevalence of microcephaly is approximately 2 cases per 1,000 live births; however, this rate varies substantially depending on the applied diagnostic criteria, the demographic composition of the study population, and the degree of inbreeding [2,6]. In populations with high rates of consanguineous marriages—a characteristic feature of several regions in Central Asia—the incidence of hereditary forms significantly exceeds global averages and can reach up to 1:1,000 [1,4]. The diagnostic evaluation of microcephaly initiates with anthropometric assessment: systematic measurement of head circumference (HC) plotted on standard percentile growth curves. A reduction in head circumference below the 3rd percentile (−2 SD), or below the 0.4th percentile (−3 SD) in severe cases, is considered diagnostically significant. Measurements must be performed dynamically at least three times to accurately evaluate the trajectory of cranial growth [3,5]. A comprehensive neurological examination encompasses the assessment of muscle tone, motor milestone development, cranial nerve functions, reflex activity, coordination, and cognitive status. For standardized neurological evaluation in infants, the Hammersmith Infant Neurological Examination (HINE) scale is highly recommended. The HINE scale comprises 26 items evaluating posture, cranial nerve functions, reflexes, muscle tone, motor skills, and behavior. The sensitivity of the HINE scale for detecting neurological abnormalities in infants with microcephaly aged 3 to 24 months reaches up to 90% [2]. For older pediatric cohorts, the Pediatric Neurological Examination (PNE) scale is utilized to quantitatively grade psychomotor and intellectual development.

OBJECTIVE

To investigate the clinical-neurological and intellectual characteristics of microcephaly across various etiological categories.

MATERIALS AND METHODS

The study enrolled 207 pediatric patients aged between 3 months and 17 years, comprising 118 girls (57.0%) and 89 boys (43.0%). Patients were stratified into three distinct groups according to the etiological form of microcephaly:

Group I (Primary Microcephaly) consisted of 95 children (45.9%); Group II (Secondary Microcephaly) included 87 children (42.0%); and Group III (Syndromic Microcephaly) comprised 25 children (12.1%).

Age distribution revealed that children aged 1–3 years and 4–7 years constituted the largest proportion across all groups, collectively accounting for 65.5% of the total cohort. This distribution reflects the typical age frame at which families seek neurological consultation for this pathology (Table 1).

Table 1. Distribution of patients by group, sex, and age

Age Group	Group I (n=95) Girls / Boys	Group II (n=87) Girls / Boys	Group III (n=25) Girls / Boys	Total n=207 n (%)
3-6 months	1 / —	1 / 1	— / —	3 (1.4%)
6-12 months	2 / —	2 / —	1 / —	5 (2.4%)
1-3 years	9 / 19	19 / 15	3 / 5	70 (33.8%)
4-7 years	21 / 11	16 / 8	5 / 6	67 (32.4%)
8-14 years	18 / 10	14 / 6	3 / 1	52 (25.1%)
15-17 years	— / 4	3 / 2	— / 1	10 (4.8%)
Total	**51 / 44**	**55 / 32**	**12 / 13**	**207 (100%)**

Note: In Group I, the difference in age distribution between girls and boys was statistically significant ($\chi^2 = 15.5$; df = 5; $p = 0.008$). In Group II: $\chi^2 = 2.61$; df = 5; $p > 0.05$. In Group III: $\chi^2 = 3.55$; df = 4; $p > 0.05$.

The mean age of patients was 6.54 ± 0.43 years (78.47 ± 5.1 months) in Group I, 5.70 ± 0.44 years (68.41 ± 5.39 months) in Group II, and 5.36 ± 0.66 years (64.32 ± 7.9 months) in Group III. Intergroup differences in mean age were statistically non-significant, confirming baseline comparability across groups.

Notably, Group I demonstrated a statistically significant male predominance in older age categories (8-14 and 15-17 years), whereas female patients predominated in the 4-7 years bracket ($\chi^2 = 15.5$; $p = 0.008$). In Groups II and III, no sex differences were observed in age distribution, pointing to specific patterns of clinical presentation and referral in primary (hereditary) microcephaly.

RESULTS

Analysis of maternal obstetric and gynecological history revealed a high prevalence of pregnancy complications across all three cohorts. Based on pregnancy and labor optimality

scales (Kainer/Palchik criteria), a compromised perinatal history was documented in 94.4% of mothers in Group I, 86.1% in Group II, and 74.0% in Group III. All parameters differed significantly ($p < 0.001$) from the healthy control group, whereas intergroup differences among microcephaly cohorts were statistically non-significant (Table 2).

Table 2. Pregnancy and labor optimality scale scores

Scale	Group I (n=95)	Group II (n=87)	Group III (n=25)	Control (n=35)
Pregnancy Optimality (Max: 35 points)	22.9 ± 1.1*	23.3 ± 0.9*	22.9 ± 1.0*	35.8 ± 1.1
Labor Optimality (Max: 17 points)	10.2 ± 0.7*	10.4 ± 0.8*	11.3 ± 0.7*	17.5 ± 0.2

Note: * Statistical significance compared to control group, $p < 0.001$.

Cranial Nerve Pathology

Manifestations of cranial nerve involvement were observed across all three groups without statistically significant intergroup variation. The most frequent abnormalities included strabismus and bulbar dysfunction. Oculomotor nerve pathology presenting as various types of strabismus was recorded in 31 patients (32.6%) in Group I, 19 patients (21.8%) in Group II, and 9 patients (36.0%) in Group III, demonstrating frequent engagement of the oculomotor system across all forms. Dysphagia was observed with comparable frequency across all cohorts (14.7%-16.1%), indicating consistent bulbar involvement regardless of etiology.

Motor Function and Muscle Tone

Motor impairments were present in all patients; however, the pattern and severity of neurological deficits differed significantly between groups (Table 3).

Table 3. Neurological status: Motor sphere and tone

Parameter	Group I (n=95)	Group II (n=87)	Group III (n=25)
Degree of Paresis:			
• Grade 1 (Mild)	6 (6.3%)	—	—
• Grade 2	18 (18.9%)	14 (16.1%)	10 (40.0%)^
• Grade 3	39 (41.1%)	47 (54.0%)	9 (36.0%)

• Grade 4	1 (1.1%)	6 (6.9%)	6 (24.0%)
• Grade 5 (Normal)	31 (32.6%)	20 (23.0%)	—
Muscle Tone:			
• Normotonia	8 (8.4%)	11 (12.6%)	4 (16.0%)
• Hypotonia	42 (44.2%)	55 (63.2%)*	1 (4.0%)***^^
• Spastic Hypertonia	45 (47.4%)	21 (24.1%)***	20 (80.0%)***^^
Tendon Reflexes:			
• Normal	25 (26.3%)	23 (26.4%)	6 (24.0%)
• Hyperreflexia	45 (47.4%)	26 (29.9%)**	19 (76.0%)***
• Hyporeflexia	23 (24.2%)	36 (41.4%)**	—
• Areflexia	2 (2.1%)	2 (2.3%)	—

Note: Differences compared to Group I: * $p < 0.01$; ** $p < 0.02$; *** $p < 0.001$. Differences compared to Group II: ^ $p < 0.02$; ^^ $p < 0.001$.

These data highlight fundamental differences in motor symptom presentation:

• In Group I, a clinical pattern of moderate paresis + spastic hypertonia + hyperreflexia predominated, with spasticity confirmed in 45 patients (47.4%) and elevated deep tendon reflexes in 45 (47.4%).

• In Group II, generalized muscle hypotonia was predominant (63.2%; $p < 0.01$ vs Group I) combined with diminished reflexes (41.4%; $p < 0.02$) consistent with white matter involvement typical of periventricular leukomalacia.

• In Group III (syndromic form), patients displayed the most severe motor deficits, marked by pronounced spastic hypertonia (80.0%; $p < 0.001$ vs Groups I and II) and hyperreflexia (76.0%), reflecting extensive corticospinal tract involvement characteristic of chromosomal disorders. Hypotonia in Group III occurred in only 1 patient (4.0%), significantly lower than in Group I (44.2%) and Group II (63.2%) ($p < 0.001$).

Intellectual Development

Intellectual disability of varying severity was observed across all patients. The degree of cognitive impairment differed significantly among groups (Table 4).

Table 4. Degree of intellectual deficit by study group

Severity Degree	Group I (n=95)	Group II (n=87)	Group III (n=25)
Mild	23 (24.2%)	11 (12.6%)*	4 (16.0%)

Moderate	24 (25.3%)	16 (18.4%)	1 (4.0%)***^^
Severe	33 (34.7%)	34 (39.1%)	13 (52.0%)
Profound	15 (15.8%)	26 (29.9%)*	7 (28.0%)

Note: Differences compared to Group I: * $p < 0.01$; *** $p < 0.001$. Differences compared to Group II: ^^ $p < 0.02$.

Group I presented a relatively balanced distribution across cognitive impairment levels, with severe intellectual disability being most common (34.7%); mild and moderate impairment comprised 24.2% and 25.3%, respectively. Group II showed a significantly higher proportion of profound intellectual disability (29.9%; $p < 0.01$ compared to Group I), whereas mild deficit was less frequent (12.6%; $p < 0.01$). Group III was dominated by severe intellectual disability (52.0%), while moderate impairment was significantly less frequent (4.0%) than in Group I (25.3%; $p < 0.001$) and Group II (18.4%; $p < 0.02$).

Pelvic organ dysfunction was recorded in the vast majority of cases: complete absence of voluntary sphincter control was documented in 72 (75.8%) patients in Group I, 76 (87.4%; $p < 0.01$ vs Group I) in Group II, and 22 (88.0%) in Group III. Nocturnal enuresis with preserved daytime control occurred in only 1 patient (1.1%) in Group I.

HINE and PNE Assessment Results

In children under 2 years of age (Group I: n=11; Group II: n=16; Group III: n=5), total HINE scale scores were 50.3 ± 2.28, 47.6 ± 1.4, and 48.8 ± 1.3, respectively. No statistically significant intergroup differences were identified, likely due to small subgroup sample sizes within this age bracket.

In children aged 2–17 years (Group I: n=84; Group II: n=71; Group III: n=20), median PNE scores were 33 (IQR: 29–43.75), 32 (IQR: 29–37), and 30 (IQR: 29–32.75), respectively. Patients in Group III achieved significantly lower scores compared to Group I ($p < 0.05$), aligning with the more severe neurological deficits in syndromic forms. The overall distribution of patients across PNE performance levels differed significantly between groups ($\chi^2 = 9.9$; $df = 4$; $p < 0.05$).

CONCLUSION

Correlation analysis between PNE scores and head circumference Z-scores demonstrated a statistically significant positive relationship in Group I ($r = 0.31$; $p = 0.004$) and Group III ($r = 0.616$; $p = 0.004$), whereas in Group II the correlation did not reach statistical significance ($r = 0.21$; $p > 0.05$). The strong correlation observed in Group III indicates that in syndromic microcephaly, the severity of head circumference reduction serves as a reliable clinical predictor of cognitive and motor deficit severity.

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