Title: Bayley- III Scores of Children with Congenital Anomalies of the Kidney and Urinary Tract

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INTRODUCTION

Congenital anomalies of the kidney and urinary tract (CAKUT) consist kidneys, collecting system or both, and arise as the result of factors affecting nephrogenesis such as maternal, placental, fetal, environmental and genetic factors. CAKUT constitute about 20 to 30 percent of all anomalies determined in the antenatal period, the overall rate of CAKUT in live and stillborn infants is 0.3 to 1.6 per 1000 (1,2). CAKUT usually progress to chronic renal disease and they are the most common cause of renal replacement therapy for end-stage renal disease (ESRD) in childhood (3). ESRD leads to growth failure and developmental delay, cognitive impairment, severe psycho-social adaptation problems, multi system complications, increased mortality and morbidity (4).

One of the usually used reliable tests for evaluation of developmental delay in children aged 1-42 months is "Bayley Scales of Infant and Toddler Development Screening Test, Third edition" (Bayley-III). This test was described in 1969 firstly, revised in 1993 and standardized in 2006 by Bayley (5). Bayley-III assesses cognitive, language and motor development of infants and children. Language scale is assessed as receptive and expressive communication, motor scale is assessed as gross motor and fine motor subscales.

ESRD is a risk factor for low IQ and academic unsuccess in schoolchild, it leads to neurocognitive developmental delay in pre-school period when rapid neurologic maturation occurs. Renal disease in early infanthood is one of the risk factors for delayed developmental outcomes (6). Differently from literature, we aimed to evaluate neurodevelopment of children who had CAKUT without ESRD by using Bayley-III test.

METHODS

Data of 30 patients with CAKUT aged between 1-41 months and 32 healthy children were included in the study. The exclusion criterias were presence of acquired urinary system anomalies, chronic neuro-muscular diseases, epilepsy, dysmorphic findings or genetic syndromes, hypoxic and/or premature birth history, neonatal hyperbilirubinemia, hypoglycemia history, and surgery history. Mersin University Ethics Committee approved the study (MEU 2016-113).

Height, weight, head circumference (HC), mid-arm circumference (MAC) had measured with standard anthropometric techniques. Left arm triceps skinfold thickness (TSF) had measured by using standard Lange calipers and anthropometric measurements recorded from patients' files. We calculated standard deviation scores (SDS) for each measurement by using standardized measures for Turkish children (7). Complete blood count, serum ferritin and urinary culture results were recorded from patients' files. Iron deficiency anemia defined as hemoglobin level <11 mg/dl, ferritin level <12 mcg/L and if these laboratory findings are not attributable to other causes (8). Urinary culture positivity ≥2 times was accepted as recurrent urinary tract infection (UTI) in patients with CAKUT (9). Newborn hearing screening was recorded as normal in all cases.

Data of the cases whose cognitive, language and motor scale scores had been evaluated with Bayley-III were studied retrospectively. Cognitive scale included thinking, learning, information processing, problem solving skills with plays and activities. Receptive communication subscale evaluated hearing, understanding, responding abilities; expressive communication subscale evaluated communication abilities using sounds, words and body language. Coordination of motor skills, sensory and perceptual motor integration, main locomotion stages were scored with fine and gross motor subtests. Composite test scores scaled as 40-160 were normal range of the Bayley-III,

mean value was identified as 100 and a standard deviation (SD) of 15. Infants had cognitive, language or global motor composite scores less than 85 were defined as developmental delay (5). An experienced and blinded to the diagnosis specialist (K.M.) performed the Bayley-III tests.

Statistical Analysis

In statistical analysis of data, number (N) and percent (%) values were given as descriptive statistics for categorical socio-demographic variables. The association between categorical variables was examined by chi-square test. Normality distribution of continuous variables was tested by Shapiro-Wilk test. Student's t-test used to test the difference between averages. ANOVA was carried out in comprasion of mean values of independent groups. The results were postulated statistically significant if *P* values were less than 0.05.

RESULTS

Data of 62 children (30 patients, 32 controls) were included in the study. Characteristic features and anthropometric measurements were shown in Table 1. The patient and control groups were similar in regard to gender, age, birth weight and maternal age (p>0.05). Mean values of height, body weight, head circumference, body mass index (BMI, kg/m^2), mid-arm circumference, and triceps skinfold thickness measurements were similar in both groups (p>0.05). Diagnoses of the patients and frequency of recurrent UTI were shown in Table 2. Mean cognitive, language, global motor scores, and mean receptive communication, expressive communication, fine motor, gross motor subscores were shown in Table 3. Mean cognitive score of the patient group was significantly lower than the control group's score (p=0.04). There was no significant difference between Bayley-III scores of the groups with or without iron deficiency anemia (Table 4). In the patient group, Bayley-III scores were statistically similar between the patients who had and hadn't recurrent UTI history. Mean cognitive

score of patients with recurrent urinary tract infection was lower than -1 standard deviation value (Table 4). Educational level of mothers that was classified as primary school, secondary school, high school and university was similar between the patient and control groups (p>0.05), and there wasn't a significant difference between Bayley-III scores of groups with regard to educational level of mothers (p>0.05).

DISCUSSION

Congenital anomalies of the kidney and urinary tract (CAKUT) are the underlying reasons in 30-50% of children who have end stage renal disease (ESRD) (3). Cognitive impairment and learning difficulties are common in children with ESRD compared to healthy peers. Attention deficit, memory and learning problems, low IQ scores are observed particularly in dialysis patients. The onset of ESRD in childhood causes more occupational and marital problems in adulthood (10). Therefore early management of CAKUT is important for preventing complications and unfavorable developmental outcomes.

Psychomotor development is affected from many genetic and environmental factors in childhood. We considered that recurrent UTIs, hospitalizations or frequent outpatient clinic controls could cause to neuromotor retardation in children with CAKUT based on the influence of chronic diseases on neurocognitive development. In this retrospective study, we evaluated neurodevelopment of normal growing children with CAKUT and without the onset of ESRD by using Bayley-III test.

We found Bayley-III scores similar in language and motor scales. Mean cognitive score of children with CAKUT was significantly lower than the control groups' mean score. Mean cognitive score of patients with recurrent urinary tract infection history was lower than -1 standard deviation

value. Febrile urinary tract infections (UTI) incidence in children with CAKUT accompanied by severe hydro-nephrosis is the highest in the newborn period and first months of life (11). This period is critical for neurodevelopment, so we consider that recurrent UTIs, frequent hospitalization and parenteral treatments due to pyelonephritis could cause developmental delay. Because hospitalizations change the enviromental factors such as materials, settings, social and physical needs that support child development. In this study we found the highest frequency of recurrent UTIs in the collecting system anomaly group, we did not find a statistically significant difference between groups with or without recurrent UTI with regard to Bayley-III scores. Although, we think that neurodevelopment of children especially with VUR or UPJ obstruction must be evaluated with larger seried studies.

The study of Demirci et al. which included 1514 Turkish children demonstrated the significant associations between maternal and paternal educational background, socio-economic status, consanguineous marriage and developmental delay in children. Elementary school or less educational level, low socio-economic status, and the presence of consanguineous marriage were assosicated with high prevalence of developmental delay in children, some other studies also verify these findings (12-13). Not finding a significantly association between Bayley-III scores with regard to maternal educational level could be explained with small sample size of our study. Presence of consanguineous marriage, paternal educational level and income level of family weren't examined in our study due to lack of data.

Presence of high quantity of iron in oligo-dendriocytes in a developing brain, iron need for energy metabolism of glial cells and negatively effect of iron deficiency anemia (IDA) on neuro-cognitive functions are known (14-15). Myelinisation, dopamine and nor-epinephrine metabolism, neuronal energy metabolism and there by child development are negatively affected by iron

deficiency (16). In our study IDA was determined in 10 patients (33%) and 10 controls (31%), a significant relationship wasn't found between IDA and low Bayley-III scores. Co-existence of CAKUT and iron deficiency anemia and its influence on child development may be investigated with the studies included larger series.

In't Wuod et al. studied maternal risk factors for CAKUT spectrum. Maternal obesity was related to increased risk of double collecting system and VUR, gestational diabetes mellitus was related to increased risk of posterior urethral valve, assisted reproductive techniques were related to increased risk of CAKUT in general (17). Torabi et al. showed a significant relationship between developmental delay in 4-60 months aged children and high maternal body mass index and gestational diabetes mellitus (18). When these results were evaluated together, we may suggest that our study should be supported with new studies which investigate development of children with CAKUT and their maternal risk factors.

Normal cognitive development depends on acquiring language and motor skills. In a study investigating the interrelationships between motor, cognitive and language development the Bayley-III test was used in 77 children with developmental delay and a strong correlation was shown between motor, cognitive and language scales when compared with results of 130 normally developing children. In conclusion, the importance of the early medical applications supporting one area development was emphasized and remembered that these applications would also contribute other areas developments (19). We also started the applications that would support development in the early period of our patients life in whom we detected cognitive delayed outcomes.

CONCLUSION

Our study contributes to literature as the first case-control study which applied the Bayley-III test in children with CAKUT, although it does not explain the direct effect of CAKUT on neuromotor development. Neurologic maturation is a process affecting from environmental and genetic factors in pre-natal, peri-natal and post-natal periods. CAKUT with recurrent UTIs may be one of the factors negatively affecting this process, severe complications like ESRD and dialysis may compromise developmentalal outcomes. Therefore it would be right to prevent recurrent UTIs and follow up the neuromotor development of children with CAKUT by using developmental screening tests since early infanthood.

The authors declare that there are not conflicts of interest.

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Table 1. Characteristics and Anthropometric Measurements of Patients and Controls

	Patient (n=30)	Control (n=32)	*P*-value
Gender			
Female (%)	16 (53)	14 (43)	0,488
Age (month)	27,58 ± 9,30	22,96 ± 9,59	0,087
Birth weight (g)	3301,6 ± 514,9	3211,5 ± 371,5	0,476
Mother's age (years)	30,8 ± 5,3	31,6 ± 5,6	0,638
Weight (SDS)	-0,03 ± 1,13	-0,11 ± 0,79	0,775
Height (SDS)	0,03 ± 1,11	0,07 ± 0,71	0,881
HC (SDS)	-0,14 ± 0,79	-0,02 ± 0,81	0,592
BMI (SDS)	-0,04 ± 1,08	0,07 ± 0,79	0,655
MAC (SDS)	-0,50 ± 0,69	-0,48 ± 0,67	0,910
TSF (SDS)	-0.17 ± 0,5	-0,02 ± 0,53	0,349

HC, head circumference; BMI, body mass index; MAC, mid-arm circumference; TSF, triceps skinfold thickness; SDS, standard deviation score.

Tablo 2. Diagnosis of the Patients and the Frequency of Recurrent UTI

Diagnosis	n (%)	Recurrent UTI n (%)
Renal parenchymal malformations	6 (20)	2 (16)
Polycystic kidney disease	1 (3)	-
Multicystic dysplasia	1 (3)	-
Renal agenesis	4 (13)	2 (16)
Anomalies of renal embryonic	5 (16)	1 (8)
migration	3 (10)	-
Renal ectopia	2 (6)	1 (8)
Horseshoe kidney	19 (63)	9 (75)
Anomalies of the collecting system	6 (20)	4(33)
Vesicoureteral reflux	11 (36)	4(33)
Ureteropelvic junction obstruction	2 (6)	1 (8)
Double collecting systems		

UTI, urinary tract infection.

Table 3. Mean Scores of Bayley-III in Patients and Controls

	Patient (n=30)	Control (n=32)	*P*-value
Cognitive	83,60 ± 8,38	100,00 ± 11,61	0,04
Language	99,92 ± 8,88	106,00 ± 13,91	0,07
Receptive communication	11,80 ± 1,60	12,23 ± 2,58	0,18
Expressive communication	9,08 ± 1,73	9,73 ± 2,70	0,31
Global motor	98,36 ± 8,73	103,46 ± 13,17	0,11

Gross motor	9,08 ± 1,68	9,69 ± 2,63	0,33
Fine motor	10,32 ± 1,97	11,53 ± 2,51	0,06

Bayley III, Bayley Scales of Infant and Toddler Development Screening Test, Third Edition.

Table 4. Bayley-III Scores with and without Iron Deficiency Anemia and Recurrent Urinary Tract Infection

	Cognitive	Language	Receptive communicatio	Expressive communicatio	Global	Gross moto	Fine moto

				n	n	motor	r	r
Controls (n=32)	With IDA (n=10,%31)	102,50 ±15,58	102,38 ±13,08	11,75 ±3,19	9,12 ±1,80	104,25 ±18,01	9,87 ±3,48	12,00 ±2,72
	Without IDA (n=22,%68)	99,16 ±9,73	107,61 ±14,32	12,44 ±2,33	10,00 ±3,02	103,11 ±11,00	9,61 ±2,27	11,33 ±2,47
	P	0,51	0,38	0,53	0,45	0,84	0,81	0,54
Patients (n=30)	With IDA (n=10, %33)	83,66 ±9,35	99,22± 8,25	11,00 ±1,65	8,66 ±1,87	96,11 ±7,67	9,00 ±1,00	9,66 ±2,12
	Without IDA (n=20,%66)	83,56 ±8,10	100,31 ±9,45	10,68 ±1,62	9,31 ±1,66	99,62 ±9,26	9,12 ±1,99	10,68 ±1,85
	P	0,97	0,77	0,65	0,38	0,34	0,86	0,22
	With RUTI (n=12, %40)	82,15 ±10,83	100,38 ±7,92	11,25 ±1,16	8,87 ±1,95	101,38 ±9,36	9,50 ±1,51	10,87 ±2,23

Without RUTI (n=18, %60)	85,05 ±7,30	99,70 ±9,52	10,58 ±1,76	9,17 ±1,66	96,94 ±8,32	8,88 ±1,76	10,05 ±1,85
P	0,09	0,86	0,34	0,69	0,24	0,40	0,34

IDA, iron deficiency anemia; RUTI, recurrent urinary tract infection.