Assessment of Cognitive Functions in Children with Chronic Renal Failure

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ABSTRACT

Background: Chronic Kidney disease (CKD) is associated with cognitive impairment. The relation between the degree of cognitive decline and severity of chronic kidney disease (CKD) is less well understood. Objective: assessment of the cognitive functions of children with CKD in comparison to age and sex matched controls as well as in relation to the degree of renal impairment, as determined by the glomerular filtration rate (GFR), subjectively by psychological assessment and objectively by ERP. Methods: In this study 25 neurologically asymptomatic children suffering from CKD of variable severity and duration were enrolled. Besides this, 25 healthy controls were also studied. Glomerular filtration rate (GFR) was estimated using the Schwartz formula. The P300 was studied in all subjects by using standard auditory ‘odd-ball’ paradigm. Stanford–Binet intelligence scale was performed. Results: We noted a significant prolongation of P300 latencies as severity of CKD increased. Duration of illness, hemoglobin level, and serum electrolytes were not correlated with P300 latency. Conclusion: Increasing severity of CKD is associated with progressive cognitive decline that can be recognized early by monitoring of P300.

INTRODUCTION

The excellent long-term survival of children with CKD is a strong motivator for optimizing neurodevelopment and educational achievement. Despite elimination of aluminum neuro-toxicity and the availability of erythropoietin therapy has eliminated two significant contributors of nervous system dysfunction in children with CKD, the neurodevelopment of those children continues to be impeded. Early assessment of cognitive function is thus recommended for all children with CKD. Testing for specific abnormalities in the domains of memory, attention, executive function and visual-spatial skills is recommended.

Auditory event related potentials (ERP), that is a recording of the electric field which the brain produces in fixed time-relation to an event, is a noninvasive method that uncovers steps of higher brain information processing. The later ERPs’ components (the ‘P300’) index information processing, attention, decisions and language.

To the best of our knowledge assessment of cognitive functions in relation to degree of renal impairment using auditory event related potentials (P300) in pediatrics was not approached. The present study aims at looking for a possible relation between P300 and the degree of renal impairment, examining whether evoked potentials can detect early subclinical CNS involvement, and verifying a possible relation between psychometric results and both P300 parameters and clinical variables.

PATIENTS AND METHODS

The study was carried out in the departments of Pediatrics, Neurophysiology and Psychiatry, Cairo University, Egypt during the period between November 2008 to October 2009. The study population included 25 patients with CKD, 14 females and 11 males, aged between 5 and 15 years. The staging of CKD was based on Schwartz formula. Primary diseases were obstructive uropathy (n=7, 28%), primary reflux nephropathy (n=5, 20%), neurogenic bladder (n=3, 12%), glomerulonephritis (n= 2, 8%), chronic interstitial nephritis (n=2, 8%), congenital hypoplastic kidney (n=2, 8%), systemic lupus erythematosus (n=1, 4%), and unknown etiology (n=3, 12%).

Clinical data were collected in the form of age, sex, height, original disease and duration of illness. Blood pressure was measured to all patients three times at the same setting of data collection and the average results were registered.

Laboratory investigations:

Hemoglobin (Hb), blood urea nitrogen (BUN), serum creatinine, sodium (Na), potassium (K),
calcium (Ca), phosphorus (P), and alkaline phosphatase (ALP) were all measured at the same setting of data collection. The reference range for Hb was 10-14.5 gm/dl, serum Na 135-148 mmol/l, K 3.5-5.3 mmol/l, Ca 9-11 mg/dl, P 4-7 mg/dl, ALP 50-644 IU/L, BUN 7-18mg/dl and creatinine 0.4-1.4 mg/dl.

Excluded from the study were all uremic children with renal replacement therapy, under the effect of drugs or any medical condition that can affect their cognitive functions and children suffering any psychiatric disorders according to Diagnostic & Statistical Manual of Mental Disorders?

Psychometric testing:

All patients were subjected to the Stanford-Binet Intelligence Scale 8 that measures intelligence and cognitive abilities in children from the age two years onwards. It consists of questions and short tasks arranged from easy to difficult to measure verbal and nonverbal skills. The test is formed of 15 subtests: 1) verbal reasoning (vocabulary, comprehension, absurdities, and verbal relations); 2) quantitative reasoning (math, number series, equation building); 3) abstract/visual reasoning (pattern analysis, matrices, paper folding and cutting, copying); and 4) short-term memory (memory for sentences, digits, and objects, and bead memory).

A formula is then used to arrive at the intelligence quotient, or I.Q. An I.Q. of 100 indicates matching between the child's chronological and mental ages. Scores of 90-109 are considered average; scores below 70 indicate mental retardation.

Neurophysiologic studies:

*Electroencephalography (EEG)*:

EEG examination was carried out on a Dantec Medtronic machine Windsor-PL EEG software 2.1. One hour of continuous recording was obtained. Monopolar and referential montages were used.

**Evoked potentials**:

Evoked potential studies were carried out on a digital MEB-9100 Version 0.3-0.6 Neuropack μ (Nihon Kohden, Japan). Two trials for each evoked potential were recorded. The means were registered for statistical analysis. All Neurophysiologic studies were carried out without the use of any sedation or hypnosis.

(i) *Auditory event related potentials*:

Auditory event related potentials were carried out using the oddball paradigm. Patients were instructed to raise the right hand as a reaction to the target tone but not the frequent one. The montage used was Cz – linked earlobes. Band pass was 0.5-70 Hz. Stimulus intensity was adjusted at 60 dB above the subject’s hearing threshold. Responses to 30 target and 120 non-target tones were obtained in each trial. The response to the infrequent tone consisted of negative (N100), positive, negative (N200), positive (P300) deflections. P300 latency was measured as the major positive peak after N200. P300 amplitude was measured from N200-P300 peaks.

(ii) *Visual evoked potentials (VEP’s)*

Pattern reversal VEP’s were carried out using 16’ checker size. Stimulation was binocular at a frequency 1 Hz. Band pass 1-300 Hz. Montage Oz-Fz. P100 wave amplitude and latency were registered.

(iii) *Brainstem auditory evoked potentials (BAEP’s)*

BAEP’s were carried out using rarefaction clicks. The stimulation was mono-aural. Montage A1 and A2 – Cz, Frequency was set at 11Hz and band pass was 1-300 Hz. I-III, III-V and I-V wave interpeak latencies were automatically computed.

Besides this, age- and sex-matched healthy controls were also studied.

The study protocol was approved by the local ethics committee, and informed written consent was obtained from the patients or their parents.

**Statistical Methods**

The data were coded and entered using the statistical package SPSS version 12. Statistical differences between groups were tested using Chi Square test for qualitative variables, student t-test for quantitative normally distributed variables and Nonparametric Mann Whitney test for quantitative variables which are not normally distributed. Correlations were done to test for linear relations between variables. P-values less than or equal to 0.05 were considered statistically significant.

### RESULTS

**Clinical data**:

The mean duration of renal impairment was 61.08±47.01 months. The means of different laboratory parameters of studied patients were as follows: BUN (mg/dl) = 59.84±23.78, GFR (ml/1.73m²/min) = 22.40±8.61, Hb (gm/dl) = 9.47±1.57, Na (mmol/l) = 140.20±5.28, K (mmol/l) = 4.42±0.74, Ca (mg/dl) = 8.61±1.42, P (mg/dl) = 4.76±1.59, ALP (IU/L) = 631.68±402.73.
Psychometric data:

There was no statistically significant correlation (p>0.05) between studied patients and control group as regard intelligence and cognitive abilities. Cognitive functions of the patients, measured by Stanford Binet Intelligence scale, were correlated significantly to P300 amplitude (p = 0.018) but not to latency or any other clinical, laboratory or electrophysiologic parameters.

Electrophysiologic data:

EEG: Twelve patients (48%) had abnormal EEG's. Diffuse background slow activity (16%), associated paroxysmal spike wave activity (16%), normal background activity with paroxysmal spike wave (16%). Thirteen (52%) patients had normal EEG.

Patient versus Control groups

A statistically significant difference was found between patient and control groups regarding the P300 latency (363.8 ± 47.496 ms versus 333.5±14.8 ms respectively, p=0.004) and amplitude (6.45±3.62 μV, versus 10.8±1.08 μV respectively, p<0.001), and the VEP latency (108±11.08 ms versus 99.8±11.07 ms respectively, p=0.012), however the VEP amplitude (14.76±6.01 μV versus 17.2±7.52 μV p= 0.207 respectively) and BAEP I-III, III-V, I-V inter-peak latencies showed non significant differences between the 2 groups (2.09±0.17 ms, 1.8±0.1 ms, 4.1±0.3 ms versus 1.95±0.31 ms, 1.88±0.4 ms, 3.9±1.1 ms p=0.059, 0.590, 0.791 respectively).

Group a versus group b:

The patients were then sub-classified into 2 groups: group A with normal EEG (n=13) and group b (n=12) with abnormal EEG.

The group a with normal EEG’s showed a significantly higher Hb level compared to those who had abnormal ones (10.81±1.47, 8.71±1.35 respectively, p=0.01), otherwise there was a non significant difference between the 2 group regarding the rest of the clinical variables, P300 and evoked potentials’ latencies or amplitudes.

Group 1 versus group 2:

The mean P300 latency of the control group plus two standard deviations (363.12 msec.) was taken as a cut off point then the patients were further re-classified into another 2 groups; group 1 (n=12) with normal P300 and group 2(n=13) with abnormal P300.

Compared to the control group P300 latency in group 1 (normal P300) showed non significant differences (p=0.130) on the other hand P300 latency in group 2 was significantly delayed (p<0.001) .

There was statistically significant higher P300 amplitude in group1 compared to group 2 (Table 1). There was a significantly higher GFR in group 1 compared to group 2 (Table1). None of the clinical variables or evoked potentials’ latencies or amplitudes showed a significant difference between the 2 groups (Table 1).

Table 1. Comparison between group 1 (Normal P300) and group 2 (Abnormal P300) regarding electrophysiologic and clinical data in children with chronic renal failure.

<table>
<thead>
<tr>
<th>Test</th>
<th>Group 1</th>
<th>Group 2</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEP latency</td>
<td>110±10.6 ms</td>
<td>105±11.36 ms</td>
<td>0.26</td>
</tr>
<tr>
<td>VEP amplitude</td>
<td>13.69±4.9 μV</td>
<td>15.77±6.87 μV</td>
<td>0.39</td>
</tr>
<tr>
<td>BAEP interpeak latency</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>I-III</td>
<td>2.07±0.19 ms</td>
<td>2.1±0.15 ms</td>
<td>0.939</td>
</tr>
<tr>
<td>III-V</td>
<td>1.87±0.32 ms</td>
<td>1.78±0.19 ms</td>
<td>0.38</td>
</tr>
<tr>
<td>I-V</td>
<td>3.94±0.3 ms</td>
<td>3.89±0.2 ms</td>
<td>0.523</td>
</tr>
<tr>
<td>P300 amplitude</td>
<td>8.0±4.3 μV</td>
<td>5.0±2.9 μV</td>
<td>0.03 *</td>
</tr>
<tr>
<td>Duration</td>
<td>6.25±4.97 mth</td>
<td>59.76±5.14 mth</td>
<td>0.888</td>
</tr>
<tr>
<td>GFR</td>
<td>27.17±9.57</td>
<td>18.0±4.53</td>
<td>0.002**</td>
</tr>
<tr>
<td>Hb</td>
<td>9.8±1.81</td>
<td>9.16±1.30</td>
<td>0.31</td>
</tr>
<tr>
<td>BUN</td>
<td>52±23.51</td>
<td>66.69±22.76</td>
<td>0.316</td>
</tr>
</tbody>
</table>

* Significant at p<0.05
** Significant at p<0.01.

BAEP brainstem auditory evoked potentials, BUN blood urea nitrogen, GFR Glomerular filtration rate, Hb hemoglobin, ms millisecond, μV microvolt, VEP visual evoked potentials.
DISCUSSION

Nervous involvement is frequent in children suffering from CKD, early recognition of cognitive decline helps providing protective measures before irreversible damage occurs.\(^7\) The P300 component of the auditory event related potentials is an objective measure of brain information processing and cognitive functions\(^9,10,11\). The latency of the P300 corresponds to the speed of cognitive processing and memory\(^12\) and the amplitude of P300 varies with the attention, on the relevancy of the task or with stimulus novelty\(^13,14\).

Compared to age matched healthy controls, P300 latency was significantly prolonged and the amplitude was significantly reduced in CKD children, furthermore within the patient group the study demonstrated a decline in cognitive function associated with increasing severity of CKD as indicated by the GFR. GFR was found to be significantly reduced in group 2 compared to group 1. The P300 amplitude as well was found to be markedly reduced in group 2. These data most likely indicate slower information processing, defective memory and reduced attention levels in group 2. Ruzicka et al.\(^15\) noted that prolongation of P300 wave latency was earliest and most evident sign of cognitive dysfunction in chronic liver disease and chronic renal failure. The non significant effect of disease duration, BUN, Hb and serum electrolytes within group (1) compared to group (2) suggests that disturbance in the level of these substances is not the cause of the cognitive decline per se. We suggest that there are certain toxins other than urea may be implicated in impairment of cognitive function in children or otherwise as suggested by Manden el al.\(^16,17\), there exists a real association between the decreased kidney function and cognition.

In this study, group 1 patients who had a mean GFR 27.17±9.57 ml/min/1.73 m\(^2\), had a normal P300 latency, compared to 18.0±4.53 ml/min/1.73 m\(^2\) in group 2 who had abnormal P300. Thus we can further support Madan’s et al.\(^18\) suggestion that patients who had a GFR greater than 30 ml/min/1.73 m\(^2\) may be free of cognitive dysfunction provided they do not have other co-morbidities.

Slowed conduction within the central nervous system was further demonstrated by the significantly prolonged VEP latency in the patient group compared to controls. Other evoked potentials’ parameters showed non significant difference in the cases versus controls. The available literature provides controversial information about relation between evoked potentials and CKD\(^6,10,18,19,20\). The variability in timing of performance of the evoked potential tests in relation to dialysis, the biochemical parameters of the uremia and the associated co-morbid conditions such as anemia may be responsible for the conflicting results. In fact the positive effects of the currently improving standards in the management of dialysis and the supportive nutrition can have a neuro-protective effect.

The non significant correlation between the psychometric test results and neurophysiologic results could be related to the different aspects that each type of test measures in respect to the cognitive functions. The two types of test should considered complementary and not alternatives.

In conclusion we can state that P300 test can be used as an objective sensitive marker for monitoring cognitive functions in children having CRF especially those showing a progressive decline in their GFR below 27.17±9.57 ml/min/1.73 m\(^2\)

[Disclosure: Authors report no conflict of interest]
**REFERENCES**


الشخصي العرabi

تقييم الإدراك المعرفي في الأطفال المصابين بانفصالية الكلى المزمن

في بعض الحيان يصاحب الفشل الكلوي المزمن فشل في الإدراك المعرفي. يهدف هذا البحث إلى تقديم هذا الفشل في الأطفال المزمن بالفحص الكلوي المزمن وعلاقته بالمتغيرات المختلفة الإكلينيكية والعملية والسريرية وآفات الفسيولوجيا العصبية. فناً تقييم 25 طفل مصاب بفشل كلوي مزمن وجمعة ضابطة من 25 طفل سليم. حسب التقييم السريري وجد 7 أطفال أقل من المتوسط أما بالنسبة لتقييم الفسيولوجيا العصبية هناك 12 لديهم نشاط غير طبيعي في زمن متوسط P300 مما وجد أنه كلاً من الفشل الإدراكي وفشل الفشل الكلوي المزمن.


Event related potentials (ERP) reflection of mental resources. Review and synthesis. Biol Psychol. 1997; 45: 19-56

