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Electrolyte changes and renal functions in children with severe malaria

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Abstract

Background: Electrolyte disturbances and renal impairment have been reported in patients with severe malaria (SM). However, the contributing mechanisms are not well identified.

Objectives: The study aims to identify disturbances in electrolytes and renal functions in children with SM and their possible pathophysiology.

Methods: The study included fifty six children with SM identified according to WHO criteria of SM. Investigations included parasitemia; glucose; urea; creatinine; sodium; and potassium estimation. Plasma osmolality was calculated.

Results: Children with SM had higher frequency of hyponatremia and hypokalemia than children with uncomplicated malaria (UM). Hyperkalemia complicated 10.7% of cases of SM. Children with SM had lower creatinine and plasma osmolality than those with UM. Children presenting with more than one of the complications, showed higher plasma osmolality, urea levels and creatinine levels than those with UM.

Conclusions: Hyponatremia may reflect the syndrome of inappropriate ADH secretion. Hypokalemia is a frequent complication while hyperkalemia complicates some cases. Dehydration may play a role in renal impairment; thus fluid therapy is indicated in cases with evidence of dehydration.

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Introduction:

Electrolyte disturbances and renal impairment were reported in patients infected with malaria parasites and were associated with severity of the disease[1-3]. However, the contributing mechanisms are not well identified. Hyponatremia is a frequent presentation in children with severe malaria and it is a serious condition in other diseases that necessitates urgent treatment. The syndrome of inappropriate ADH secretion[3], renal impairment[4]. and dehydration are among the suggested mechanisms with controversial findings[1, 2]. On the other hand, potassium changes were also reported and were linked to acid- base balance status[5, 6].

This study investigated serum electrolytes and renal functions in children infected with malaria parasite to identify abnormalities and possible mechanisms.

Methods:

The study was a cross- sectional study, conducted at Wad Medani Pediatric Hospital. The collection of samples started in September 2007 and extended up to September 2008.The study included a cohort of fifty six children with severe malaria according to WHO criteria of SM. [7]Thirty one children with UM were included in the study for comparison. The age of both groups ranged from 2 to 12 years.

Exclusion criteria were as follows: patients who had antimalarial treatment before admission and those who were known to have renal disease; hepatic disease; and diabetes mellitus. Patients suffering from metabolic and developmental disorders; malnutrition; pneumonia; septicemia; meningitis; congenital heart diseases; HIV infection; and tuberculosis were also excluded.

The study was approved by the Institutional Ethical Committee of the University of Khartoum and informed written consent was obtained from children's parents.

History and physical examination: Both groups of patients underwent history taking and comprehensive physical examination by the researcher and hospital staff. A data collection form was completed for each patient including history and physical examination.

Malaria diagnosis and blood tests: A sample of 5 ml was taken from each patient on admission and before treatment was started and divided into 3 tubes: one containing EDTA was used for parasitemia estimation. The second tube was a plain tube which was used for urea, creatinine, sodium and potassium estimation. The third tube containing fluoride was used for random blood glucose (RBG) estimation.

The microscopic identification of the malaria parasite was the method of confirmation of infection with *plasmodium falciparum* used in the study to satisfy WHO criteria. Only positive cases were included. The thick blood film was used for parasite detection while thin film was used for identification of species and parasitemia estimation.

The thin blood film was fixed using absolute methyl alcohol, and then stock solution of Giemsa stain was diluted with distilled water. The distilled water was kept at pH 7.1-7.2 using phosphate buffer. Staining of films was done. Parasitemia estimated in thin films expressed as a percentage of infected RBCs from total RBCs[8].

Urea was measured by a UV enzymatic method using spectrophotometer[9]. Creatinine was measured by a colorimetric enzymatic method[10]. Sodium and potassium were measured in serum samples using a flame photometer[11]. RBG was measured by enzymatic colorimetric method[12].

Plasma osmolality was calculated using the following formula[13].

Plasma osmolality (mosm/l) = 2×sodium (mmol/l) + 0.055× urea (mg/dl) + 0.36 × glucose (mg/dl).

Statistical analysis: Statistical analysis was carried out with Statistical Package of Social Sciences (SPSS) for windows version 11.5. Normality of data distribution was checked using Kolmogrov-Smirnov test. Homogeneity of data was checked by the Levene's test for equality of variances. Data were presented as means and standard deviations and analyzed by student's *t* test. Correlations were compared using the χ^2 tests if the variables were qualitative. Pearson's correlation coefficient was used for quantitative variables and Spearman' rank correlation coefficient tests was used to correlate quantitive variable with qualitative variable. P values < 0.05 were considered as significant.

Results:

Clinical presentations: twenty three patients presented with repeated convulsions, thirteen patients presented with cerebral malaria and an equal number with severe anemia. Some patients presented with hemoglobinuria (n=2), hypoglycemia (n= 1) and some with more than one complication (n= 4).

Laboratory findings: Children with SM showed significantly lower mean creatinine level than those with UM (table-1).

The mean urea level in uncomplicated malaria was 22.78mg/dl while in severe malaria it was 25.14mg/dl. No significant difference was found between the two (P value=0.398). Significant difference was found with mixed presentations (UM=.22.78±6.14 versus 55.00±39.54 P value=0.000)

The mean creatinine level in uncomplicated malaria was 0.56mg/dl while in severe malaria it was 0.40mg/dl. A significant difference was found

between the two (P value=0.016) as well as with other severe malaria categories (Table 2)

The mean sodium level in uncomplicated malaria was 135mmol/l while in severe malaria 133mmol/l no significant difference was found between the two. However, a total of fifty children were found to be hyponatremic, most of them had severe malaria. Incidence of hyponatremia was more frequent in severe malaria than uncomplicated malaria (P value=0.005).

Plasma osmolality was lower in children with severe malaria than in those with UM with exclusion of mixed presentations (Table 3) and in some severe malaria categories (Table 4).

Although the mean potassium level in uncomplicated malaria showed no significant difference compared with severe malaria, hypokalemia was found to be significantly more frequent in severe malaria than uncomplicated malaria (P value=0.039) (Figure-1). Some children showed hyperkalemia and presented mostly with neurological manifestations in the form of cerebral malaria or repeated convulsions and one of them died.

About 30.4% of children with severe malaria were found to have hyperparasitemia while 19.4% of those with uncomplicated malaria had hyperparasitemia. The incidence of hyperparasitemia was significantly more in severe malaria than in uncomplicated malaria (P value=0.022). No significant correlation were found between the degree of parasitemia and potassium (P value=0.298) or sodium (P value=0.244).

Table1. Laboratory investigations of patients with uncomplicated malaria (UM) & severe malaria (SM)

Investigation	Kolmogrov-Smirnov test P value	UM (mean± SD)	SM (mean ±SD)	P value
Urea(mg/dl)	0.076	22.784±6.14	25.14±14.72	0.398
Creatinine(mg/dl)	0.063	0.561±0.22	0.40±0.32	0.016
Na+(mmol/l)	0.200	135.03±3.30	133.20±4.65	0.056
K+(mmol/l)	0.067	3.84±0.41	3.98±1.04	0.474
Random blood glucose(mg/dl)	0.367	108±39.14	89.27±39.06	0.035

Table2. Comparison of creatinine between UM& SM categories

UM	SM categories	Number	Mean ±SD	P value
0.56±0.22	Cerebral malaria	13	0.41±0.21	0.054
	Severe anemia	13	0.36±0.22	
	Repeated convulsions	23	0.36±0.15	
	Hypoglycemia	1	0.10	
	Hemoglobinuria	2	0.20±.00	
	Mixed presentations	4	0.90±.94	0.082

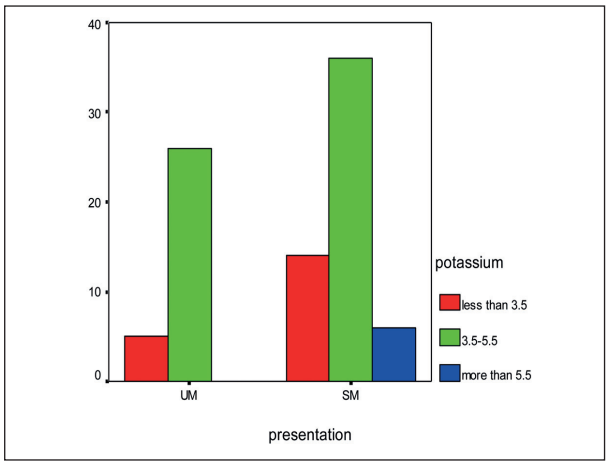
Table3. Comparison between osmolality in UM and SM cases (without mixed presentations)

UM	Number	Mean ±SD	P value
UM	31	6.9±284.2	0.007
SM	52	9.7±279.18	

Table 4. Comparison of plasma osmolality between UM& SM categories

UM	SM categories	Number	Mean ±SD	P value
284.± 6.9	Cerebral malaria	13	281.710.9±	0.36
	Severe anemia	13	276.88.7±	0.005
	Repeated convulsions	23	278.69.5±	0.016
	Hypoglycemia	1	286.96.9±	0.69
	Hemoglobinuria	2	280±.16.	0.43
	Mixed presentations	4	295.616.0±	0.251

Figure-1 Incidence of hypokalemia and hyperkalemia in UM & SM



Discussion

The present study reports children with severe malaria suffered from hyponatremia, hypokalemia and low creatinine level and low plasma osmolality. These could have well been due to inappropriate ADH secretion. No correlation was detected between the sodium level and degree of parasitemia.

Although the literature commonly reported sodium changes in malaria, the contributing mechanisms are not well identified. Possible mechanisms are: syndrome of inappropriate ADH secretion; renal impairment; and dehydration[1]; cerebral salt wasting[2]; renal losses[14]; and the "sick cell syndrome. [15] A study carried on Kenyan children detected hyponatremia in 53% of children with SM. Hyponatremia was not related to peripheral parasite density, dehydration and abnormal renal function. ADH was found to be inappropriate to the degree of dehydration. [3] However, some studies detected appropriate ADH secretion in patients with hyponatremia. [1, 2]

Renal impairment was reported as a cause of hyponatremia in malaria. [1, 4] Hyponatremia was associated with increased urinary sodium concentration in the presence of reduced creatinine clearance in these patients.[4] In this study, the mean plasma urea level in children with SM was normal and not significantly different from children with UM. The mean creatinine level was significantly low in children with SM most likely reflecting the diluted plasma as a result of inappropriate ADH secretion. This study did not show evidence of renal impairment thereby it is not the explanation of hyponatremia in the study cases.

In the present study the incidence of hypokalemia was more frequent in children with SM than in

those with UM. Hyperkalemia was detected in 10.7% of children with SM and most of them had neurological manifestations.

Alteration in potassium is associated with acidemia and alkalemia. A study carried in thirty eight Kenyan children with severe malaria and acidosis detected that at admission, serum potassium was normal in 31 (81.6%), low in 4 (11%) children and 3 (6.3%) children had hyperkalaemia. Plasma potassium decreased rapidly after correction of acidosis. Fractional excretion of potassium and the trans-tubular gradient of potassium were above normal range, indicating renal potassium loss and the study concluded that hypokalaemia was a common complication of severe malaria. However, it was often not apparent on admission. The plasma potassium decreased precipitously after correction of acidosis, and thus serial monitoring of serum potassium was suggested in patients with severe malaria complicated by acidosis. [5] Hyperkalemia was reported in malaria cases complicated by acidosis and was associated with increased mortality, generally soon after admission[6].

The present work showed that mean urea levels were nearly the same in SM and UM. Children with mixed presentation had significantly higher urea level than those with UM. They also had relatively higher creatinine, higher sodium and higher plasma osmolality in comparison with UM and other SM categories. They also had higher body temperature, higher incidence of tachycardia and tachypnea than UM and other SM categories. These findings suggest that dehydration might play a role in this subgroup of SM and that dehydration was an indicator of poor outcome in children with SM as this group of children had increased morbidity. Mild renal impairment was reported in children with malaria and dehydration was known as a contributing factor. [4, 1, 5] Maitland et al (2003) found that volume expansion in children with dehydration was associated with correction of the hemodynamic abnormalities and improvement of organ functions. [16] Therefore, volume resuscitation should be considered in severe malaria with evidence of dehydration.

Acute renal failure is seen mostly in *Plasmodium falciparum* infection, but *P vivax* and *P. malariae* can occasionally contribute to renal impairment. [17, 18] Malarial ARF is commonly encountered in non-immune adults and older children with *falciparum* malaria in areas of low endemicity. Several hypotheses including: mechanical obstruction by infected erythrocytes; immune- mediated glomerular and tubular pathology[19, 20]; fluid losses due to multiple mechanisms; and alterations in the renal microcirculation have been proposed[18, 21-23]. Renal impairment on admission carries a poor prognosis even though acute renal failure is rare in children[24, 25].

In this study creatinine was significantly lower in children with SM than in those with UM. This finding can be explained by the inappropriate ADH secretion which was reported to occur in SM[3].

Conclusions:

The findings of this study showed that electrolyte changes are common in malaria. Hyponatremia most probably reflects the syndrome of inappropriate ADH secretion (SIADH) . Potassium changes ranged from hypokalemia to hyperkalemia. Dehydration may play a role in renal impairment encountered during malaria infection.

It appears that fluid therapy is needed only in the subgroup of the infected children who showed evidence of dehydration. While those with hyponatremia may not need fluids therapy and close observation may be the only action needed.

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Authors' contribution:

Dr Nisreen had contributed to the design of the study, collection and analysis of the data, wrote the paper and approved the final version of the manuscript. Professor MY Sukkar had contributed

to the design of the study, analysis of the data, and critical revision of the paper and approved the final draft.

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Reference Values of Facial Nerve Stimulation Using Nerve Conduction Study

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Abstract:

Background: Electroneurography (ENoG) is an objective electro-physiologic measurement used to assess facial nerve integrity; determine the prognosis of facial nerve injury; and guide management.

Objective: This study aimed at establishing baseline reference values of facial nerve parameters of compound muscle action potential (CMAP) for comparison with abnormal findings of facial nerve disorders.

Methods: This cross-sectional study was conducted at the Physiology Department, Faculty of Medicine, University of Khartoum. It involved sixty healthy volunteers (25 males & 35 females). Their mean age was (34.1±15.98), ranged (15-65years). Pre-auricular stimulation of the facial nerve and recording from Nasalis muscle was done bilaterally using Medelec Synergy Machine.

Results: The distance between stimulating and recording electrodes ±SD was 0.65±٨,٢١ cm (7.56–8.86cm). Nerve conduction study findings showed values of total right & left (120) facial nerves as well as right and left sides values including (minimum, maximum, mean and standard deviation) of latencies, amplitudes, durations and areas of facial CMAP.

Conclusion: The values for parameters of facial nerve stimulation are comparable to that of worldwide literature. The variations observed here were most likely due to many factors such as: stimulating electrode placement (pre-auricular versus post-auricular); recording electrodes placement (using different muscles innervated by facial nerve); skin resistance; and magnitude of stimulus.

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Interoduction:

Electroneurography (ENoG), an objective electro-physiologic measurement of compound muscle action potential (CMAP), is used to assess the integrity of a peripheral motor nerve [(1)]. It is a quick, relatively painless procedure for assessing facial nerve function [(2)]. Electroneurography (ENoG), also is referred to as evoked electromyography (EEMG) and electroneuronography, involves electrical stimulation of the facial nerve with simultaneous electromyographic (EMG) recording[(3)]. Electroneuronography (ENoG) and electromyography (EMG) are the objective tests of facial function most useful in determining the prognosis of facial nerve disorders and in guiding treatment. They are both electro-physiologic measures that indirectly quantify facial nerve function by recording motor unit action potentials (MUAPs) and/or compound muscle action potentials (CMAPs) [(2)]. EMG showed higher prognostic values than ENoG, especially when repeated during the time course of the facial palsy; but ENoG might be helpful if the EMG result is not classifiable[(4)]. Although stimulation electromyography was introduced by Gilliat and Taylor [(5)] as early as in 1959, it was Esslen [(6)] who pioneered this as a test for facial nerve function.

The technique offers the distinct advantage over

previous methods of providing an objective quantitative assessment of facial nerve function. The latency, amplitude and total duration of the CMAP are the important parameters of evoked EMG. The technique relies on comparing these values obtained from the affected side with that from the normal side in unilateral facial palsy.

Many other alternative tests of facial nerve function have been, and continue to be, used [7]. These include: the Hilger test; acoustic reflex testing [8]; evoked accelerometry; antidromic nerve potentials; MRI and CT radiologic evaluations; maximal nerve stimulation tests; minimal nerve stimulation tests; trans-cranial magnetic stimulation [9]; blink reflex tests [10] ;and highfrequency ultrasonography (HFUS) as a complementary technique paired with neural electrophysiology was beneficial in the evaluation and prognosis of Bell's palsy disease [11]. Blink reflex and ENoG, considered together with clinical findings, could offer a good indication and best predictors of facial function recovery in the first phases of Bell's palsy, while EMG findings did not add any prognostic significance [12].

Anatomically the facial nerve is the seventh cranial nerve. It carries motor, secretory, and afferent sensory fibers from the anterior two thirds of the tongue. Its nucleus is located within the central nervous system in the pons. This nerve provides motor innervations to the muscles of facial expression, i.e. all facial muscles except those innervated by the trigeminal nerve (masseter, temporalis and pterygoid muscles). Each facial nerve has some 10,000 fibers. About two thirds of the fibers are motor, while only one third are sensory. The anatomic course of the facial nerve can be separated into an intracranial and extra-cranial portion. Intra-cranially, the seventh nerve arises from the pons and traverses the cerebello-pontine angle (CPA) to enter the facial canal via the internal auditory meatus (i.e. the porus-acousticus). The facial canal consists of the labyrinthine, tympanic, and mastoid segments, of which the labyrinthine is the smallest. The mastoid segment terminates, and finally, exits the skull through the stylo- mastoid foramen to begin its extra-cranial course. As the main trunk of the facial nerve enters the parotid region, it divides into superior and inferior divisions from which five main branches arise (temporal, zygomatic and buccal, mandibular and cervical) just anterior and inferior to the tragus of the ear. It innervates various muscles of facial expression [1, 3, 7, 13]. These muscles are relatively easy to evaluate with nerve conduction techniques because of their superficial location.

There are various etiological factors for facial nerve paralysis, the most common of which is Bell palsy, which is unilateral and is considered to be of idiopathic etiology. The other causes are metabolic: (e.g. diabetes mellitus); traumatic; neurologic; infectious; vascular; toxic; neoplastic; iatrogenic; and idiopathic [3, 7, 14-16].

The evaluation of facial nerve viability by means of electroneuronography (ENoG) is critically important in the management of facial nerve disorders. Depending on the outcome of the ENoG evaluation, the physician may choose to "watch and wait" or may decide to intervene surgically [7]. Hence, this test is usually done in cases of unilateral facial nerve paralysis to compare the neurophysiological responses of the normal facial nerve to that of abnormal one. The idea behind doing this is to determine whether surgical intervention is recommended or not, and also to decide the prognosis. The present study was undertaken in normal subjects to establish the normal parameters of facial nerve stimulation (latency, amplitude, duration and area) among Sudanese population and consider these results as baseline reference or cut- off values for comparison with the abnormal findings in cases of facial nerve dysfunction. Our study is the first to establish reference values of facial nerve stimulation in Sudan. Unavailability of the test in most of our centers makes prediction of prognosis of facial nerve dysfunction extremely difficult leading to deficient management of facial nerve palsies.

Methods:

This prospective cross- sectional study was conducted at the Department of Physiology, Faculty

of Medicine, University of Khartoum, during a six months period. The study was carried out on healthy human volunteers who were mainly selected from medical students and workers in the Faculty of Medicine and area around it. Sixty subjects participated in this study of whom 25 were males and 35 were females. Their ages ranged from 15-65 years. Only healthy subjects were included in the study (i.e. they had been subjected to thorough history taking and clinical examination). Individuals with a history of facial paralysis due to any cause, neuromuscular disorders (e.g. Gilllain-Barre syndrome), injury, trauma to the temporal bone secondary to motor vehicle accidents (MVA), recent infections (otitis media, mastoiditis, mumps, chicken-pox, herpes zoster oticus), central nervous system disorders (e.g. Multiple sclerosis, stroke), drugs causing peripheral neuropathy, alcohol consumers and diabetics were excluded from the study. Data collection was performed using questionnaire that was designed taking into consideration the full medical history with reference to age, sex and occupation. General physical and neurological examination was done for all volunteers.

The test was performed using Medelec Synergy Machine. The skin was prepared for application of the stimulating and recording electrodes. The subject was made to sit down on a chair while the test was carried out. The stimulating electrode in this study was placed directly over the facial nerve anterior to the earlobe (pre-auricular). The cathode is placed just anterior and inferior to the tragus of the earlobe. Slight manual superior/inferior movement was required to optimally locate facial nerve stimulation position that generates the best compound muscle action potential. The active recording electrode was placed over the Nasalis muscle belly [17] (lateral mid-nose) 1-2 cm above the external naris; sometimes the subject needed to wrinkle the nose and the electrode was placed on the most prominent bulge of the muscle while the reference electrode was placed in the same position on the other side of the face, or on the tip or bridge of the nose [13, 18]. The ground electrode was placed on the chin. The current intensity was increased from zero to a level sufficient to evoke maximal CMAP. An additional 10%-20% of current was added to produce supra-maximal stimulation [2, 13]. A single supra-maximal stimulus was applied to the facial nerve and an individual(CMAP) response was recorded from Nasalis muscles. The CMAP response was recorded first on the right side and then on the left side. Therefore, measurement was conducted using the same technique and distance. From the trace displayed on the monitor, latency, amplitude total duration and area of the CMAP were measured automatically by the digital machine. Latency was measured in milliseconds from the start of the stimulus artefact to the onset of muscle response. Total duration of the response was measured in milliseconds and area in mv/ ms from the beginning to the end of CMAP. Amplitude was measured in millivolts. Finally, the distance between the cathode stimulating and the active recording electrodes was measured in centimeters [13, 18]. Three trials were made for reproducibility on each side of the face and the best was considered.

Statistical analysis was performed using the Statistical Package for Social Science (SPSS) program. The study was ethically approved by the Ethics Research Committee of the Faculty of Medicine , University of Khartoum. All participants were fully informed about the test. They signed an informed consent to volunteer to the research and they had the freedom to withdraw from the study at any time.

Results:

Sixty normal volunteers were included in the study. Gender distribution showed a percentage of 58.3 females and 41.7 males. Age (mean ± SD) was 34.1 ± 15.98 years. Nerve conduction study findings showed values of total right and left parameters of facial nerve stimulation (120 nerves) including mean and SD of the latencies, amplitudes, durations and areas of the CMAP which were summarized in (table 1). In addition, values of right facial nerves and left facial nerves CMAP parameters were illustrated for each nerve separately in (table 2). The

mean distance between stimulating and recording electrodes ± SD was found to be 8.21 ± 0.65 cm, ranged (7.56 – 8.86 cm).

Stimulation of the facial nerve anterior to the ear lobe revealed a mean onset latency of 2.87 ± 0.56 ms (2.31-3.43ms) for total right and left facial nerves; mean value of right side latency was 2.83 ± 0.51 ms and left side 2.91 ± 0.61 ms. The mean amplitude was 2.74 ± 1.12 mv (1.63-3.87 mv) for total right and left facial nerves; mean value of right side amplitude was 2.43 ± 0.98 mv and left side 3.05 ± 1.16 mv. The mean response duration was 11.45 ± 1.89 ms (3.22-27.12 ms) for total right and left facial nerves; mean value of right side unit duration was 12.43 ± 2.15 ms and left side 10.47 ± 1.6 ms. The mean response area was 12.48 ± 2.15 mv/ms (4.17-29.13 mv/ms) for total right and left facial nerves; mean value of right side response area was 12.26 ± 2.68 mv/ms and left side 12.7 ± 1.46 mv/ms.

Table 1. Summary of Reference Values of CMAP **Table 1. Summary of Reference Values of CMAP parameters for total right and left facial nerves (n=120) in healthy individuals**

CMAP parameters of total Rt & Lt facial nerves	N	Mean	SD	minimum	maximum
Rt & Lt Latencies (ms)	120	2.87	0.56	2.31	3.43
Rt & Lt Amplitude (mv)	120	2.74	1.12	1.63	3.87
Rt & Lt Duration (ms)	120	11.45	1.89	3.22	27.12
Rt & Lt Area (mv/ms)	120	12.48	2.15	4.17	29.13

Table 2. Summary of Reference Values of CMAP parameters for individual right facial nerves (n=60) and left facial nerves (n=60) in healthy individuals

CMAP parameters of facial nerve	N	Mean	SD
Rt Latency (ms)	60	2.83	0.51
Lt Latency (ms)	60	2.91	0.61
Rt Amplitude (mv)	60	2.43	0.98
Lt Amplitude (mv)	60	3.06	1.16
Rt Duration (ms)	60	12.43	2.15
Lt Duration (ms)	60	10.47	1.6
Rt Area (mv/ms)	60	12.26	2.68
Lt Area (mv/ms)	60	12.69	1.46

Discution:

Electrical stimulation has been used by neurophysiologists over years to test motor nerve function. In recent years, the precision of such tests has been greatly increased by the recording of compound muscle action potentials as a measure in a number of neuromuscular disorders. Almost every aspect of this type of response might be useful in diagnosis [19]. In the present study, individual CMAP from Nasalis muscles were recorded on both sides of the face. Response latency is largely a measure of the time required for a nerve action potential to travel down the nerve plus neuromuscular transmission time and muscle fiber depolarization time. Since the latter two are relatively constant, changes in latency reflect changes in nerve conduction time [13, 20]. Amplitude of the CMAP is roughly proportional to the number of muscle fibers that respond to the nerve impulse, which in turn correlate with the number of intact motor neurons [13]. The duration of CMAP, measured from the beginning to the end of CMAP, is related to the difference in conduction time in the various axons and muscle fibers. It reflects the synchrony of contraction of the muscle fibers contributing to the response [13].

In this study stimulation of the facial nerve anterior to the ear lobe (pre-auricular) showed mean values for CMAP parameters (latency, amplitude, duration & area) using distance that ranged between (7.56-8.86 cm). Our mean latency of **2.87 ± 0.56** msec which ranged (2.31 -3.43) was lower compared to 3.57 ± 0.35 msec (2.8-4.1) in which facial nerve stimulation was pre-auricular [18]. Again it was lower than 3.880.36± msec (3.2-4.4) in which facial nerve stimulation was post-auricular [18]. Another study reported mean latency of 3.5 ± 0.4 msec in which post-auricular stimulation of the facial nerve was carried-out [13, 21]. These variations might reflect differences in the placement of stimulating and recording electrodes. In a similar Indian study done in 2003 on 45 normal subjects in the age group of 20–30 years, a mean value of latency on the right side was found to be 3.51 ± 0.38 msec and on left side 3.45 ± 0.49 msec [22]. Their latencies were greater than ours (**2.83 ± 0.51** ms in the right and **2.91 ± 0.61** ms in the left side). That could be explained by their longer distance between stimulating electrodes (stylo-mastoid foramen behind the ramus of the mandible) and recording electrodes (alae-nasi) used in that study [22]. An increase in distance of 1 cm between the stimulating and recording electrodes results in an increase in latency of 0.23 msec [23].

The mean CAMP amplitude of the current study was found to be **2.74 ± 1.12,** and ranges between (**1.63 - 3.87** mv) which is in agreement with other reported reference values range from (1-4 mv) [13]. The Indian study findings of facial nerves amplitudes of the right side (2829.26 ± 918.07 µv) and the left side (2989.13 ± 1073.62 µv) were comparable to ours (**2.43 ± 0.98** mv on the right side & **3.05 ± 1.16** mv on the left side) because of the use of similar stimulation techniques [22]. Electro-diagnostic evaluation of the temporal branch of the facial nerve and establishment of normative values was done by Silva et al [24]. They studied 150 healthy volunteers stimulating the facial nerve at two points along the nerve course, distal: (on the temple, over the temporal branch) and proximal: (in retro-auricular region) on both sides of the face and recording from the ipsilateral Frontalis muscle. Their variable amplitudes obtained [ranging from 0.20 to 3.20 mV for the distal stimulus, and 0.20 to 2.7 mV for the proximal stimulus] were slightly lower compared to our range (**1.63-3.87** mv) of 120 CMAP amplitudes.

Our results of mean CMAP duration were **11.45 ± 1.89** ms for total right and left facial nerves, **12.43 ± 2.15** ms for the right side and **10.47 ± 1.6** ms for the left. These values were greater than those reported by the Indian study [22] for total duration of right side CMAP (5.03 ± 1.48 msec) and left side CMAP (5.22 ± 1.54 msec). The duration of CMAP is related to the conduction velocities of large diameter motor nerve fibers and reflects the synchrony of discharge of individual muscle fibers [13, 25]. CMAP duration is measured either from beginning to end of the response (total duration) ,or from the initial onset to the final return of the negative deflection (negative–

peak duration) ;and usually the peak duration is about 30% of the total duration in normal control. This fact may explain our longer total duration compared to the Indian study duration [25]. The use of different muscles for recording (Frontals vs. Nasalis) might had partially contributed to this variation as well as different electrode placement would result in different waveforms [26].

Conclusion:

Facial electroneuronography can be performed reliably in the clinic and is usually well tolerated and is of great value in assessing facial nerve's functional integrity. The values for parameters of facial nerve stimulation in our study are comparable to those of world-wide literature. The variations observed were most likely due to many technical factors such as: electrode placement of both stimulating electrodes (pre-auricular vs. post-auricular) and recording electrodes (different muscles innervated by facial nerve); skin resistance ;and magnitude of stimulus intensity.

Recommendation:

Since this is the first study in Sudan establishing nerve conduction studies normal values of facial nerve stimulation, we recommend doctors and neuroscientists to use these normal parameters in the evaluation of patients with facial nerve dysfunction.

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Haemoglobin A1c level in non-diabetic patients with end- stage renal disease on haemodialysis

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Abstract

Background: Haemoglobin A1c(HbA1c) is widely used to monitor the glycaemic control in diabetic patients. Recently, it has been found useful for the diagnosis of diabetes mellitus. High HbA1c is said to be associated with high risk of coronary vessel disease irrespective of diabetes.

Objectives: to measure HbA1c concentration in patients with end-stage renal disease on haemodialysis and to correlate its concentration with the duration of disease and total cholesterol level.

Methods: sixty non-diabetic patients with end-stage renal disease on haemodialysis were included in the study. They were matched for sex and gender with sixty apparently normal controls.

Results: there was a significant increase in HbA1c concentration in the study group when compared with the controls with a mean HbA1c concentration of 5.67% +0.2 (P-value= 0.000). There was a significant positive correlation between the HbA1c level and the duration of the haemodialysis (p-value<0.05). A strong correlation was found between Hb A1c and the total cholesterol concentration (p-value< 0.05).

Conclusion: Hb A1c is higher in patients with end-stage renal disease when compared with normal controls. The increase in HbA1c correlates with the duration of the haemodialysis and the cholesterol level.

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Introduction:

HbA1c is a haemoglobin compound produced when glucose reacts with the amino group of haemoglobin. The rate of formation is directly proportional to the plasma glucose concentrations[(1)]. It is widely used to monitor the glycaemic control in diabetic patients. A level <7% indicates optimum control[(3)].

Recently, HbA1c has been found to be useful for the diagnosis of diabetes mellitus. A level of > 6.5% is recommended for the diagnosis of diabetes mellitus[(4)].

Another factor that determines HA1c concentration is the red cells life span. Patients with haemoglobinopathies tend to have a lower concentration of HbA1c[(1)].

Some studies have implicated HbA1c level as an independent risk factor for cardiovascular events and the development of atherosclerosis, independent of diabetes status.[(5,6)]

A study by Khaw et al. demonstrated that a raised HbA1c level predicted mortality and cardiovascular disease in patients without diabetes in the community. Persons with HbA1c concentration < 5% had the lowest rate of coronary vascular disease (CVD) and mortality.

End-stage renal disease is a major health problem, with serious implications on the health system and increased morbidity and mortality. Worldwide, it has a prevalence of 1.1 million[8]. In Sudan the incidence is 70-140/million inhabitants/yr[(10)].

Reduced kidney function is recognized as a powerful and independent risk factor for CVD, even after

adjusting for age and diabetic status[11].

Some studies have shown that HbA1c can predict future CVD events among non-diabetic patients in the general population, and it may play a role in risk stratification and early identification of patients with non-diabetic CKD and at risk of developing CVD[12]. The risk for CVD and overall mortality increased continuously with the HbA1c concentration[13].

Some studies found that the average HbA1c level in non-diabetic end-stage renal disease (ESRD) patients receiving haemodialysis was higher than in healthy individuals[14, 15].

It was found that patients with ESRD have higher levels of cholesterol, which correlates with the duration of haemodialysis[16], and it is well-known that hypercholesterolemia is closely linked to CVD[17].

The aim of this study was to estimate the level of HbA1c in non-diabetic patients with end- stage renal disease on haemodialysis and correlate it with the duration of ESRD and total cholesterol concentration.

Materials and Methods:

A cross-sectional, hospital-based study was carried out in Ibn Sina Renal Dialysis Centre and the Academic Charity Hospital. Sixty non-diabetic chronic renal failure patients on haemodialysis were enrolled in the study, together with 60 apparently healthy matching controls. The study was approved by the Research Committee in the University of Medical Sciences and Technology and a written informed consent was taken from all participants. Results of the HbA1c and cholesterol concentration were shown to all participants.

Patients with: diabetes mellitus, anaemia, and on steroids were excluded from the study.

A questionnaire was used to collect the data. Study variables included: age; gender; and duration of renal failure; history of diabetes and drug history. Haemoglobin, mean corpuscular cell volume (MCV) and mean corpuscular haemoglobin (MCHC) were collected from the patients' records.

Venous blood samples for HbA1c were collected in ethylene diamine tetraacetic acid (EDTA) containers. Samples were stored in 2-4 C until time of analysis which was not more than 4 days after collection. Whole blood was used for the analysis. HbA1c was measured by affinity chromatography which is the preferred method in the clinical laboratory. In this method, the glycoselated haemoglobin attaches to the boronate group of the resin and is selectively eluted from the resin bed using a buffer. This method is not temperature- dependant and is not affected by other types of haemoglobin.

Plasma total cholesterol was measured by the cholesterol oxidase method. Venous blood was collected in heparin containers and plasma was separated by centrifugation. Samples were stored at 2-4C until time of analysis.

Data was entered into SPSS version 13 for analysis. A frequency table was constructed regarding the study variables. The HbA1c and total cholesterol of the study groups were presented in mean and standard deviation. Pearson correlation and student t-test were used for testing the significance of the results.

Results:

The study population consisted of 45 males and 15 males. The age distribution showed that 31.7% were in the age group of 20-40; 53.3% were 41-60 years; and 25% were more than 60 years old.

The mean HbA1c concentration in the non-diabetic patients with end-stage renal failure was 5.7% which is significantly higher than that of the controls 5% (p value 0.000) Table 1.

Table 1. Mean HbA1c concentration

Subjects	Mean concentration	SD	P value
Cases	5.7%	0.2	0.000
Controls	5%	0.4	

Regarding the cholesterol concentration, it was significantly higher in the study group (111.6 mg/dl) than in the controls (96.7mg/dl) with a P value of 0.004 as shown in Table 2.

Table 2. Mean serum cholesterol concentration

Subjects	Mean concentration	P value
Cases	111.6 mg/dl	0.004
Controls	96.7 mg/dl	

As shown in table 3 , significant correlation between the HbA1c concentration and the cholesterol concentrations was found (P value 0.007). There was a significant correlation between the HbA1c concentration and the duration of the haemodialysis (P value 0.041); however, serum cholesterol did not show a similar correlation

Table 3. Correlation between the duration of ESRD and HbA1c and cholesterol concentrations

Duration of ESRD	Pearson correlation	P-value
HbA1c conc.	0.265	0.041
Cholesterol conc.	0.095	0.470

Discussion

In this study it was found that the HbA1c level was significantly higher in the ESRD patients than in the controls. This finding was consistent with similar previous studies. One study found that the average HbA1c level in non-diabetic end-stage renal disease (ESRD) patients receiving haemodialysis was 5.99% and in the control group was 5.45% ($p<0.05$).14 Another study found that in non-diabetic control patients, the HbA1c level was 4.56 %+ 0.52 and in ESRD patients, the HbA1c level was 5.23%+1.16 ($p <0.001$)x[15]. Thus, there was a significant elevation of HbA1c levels in non-diabetic ESRD patients who received haemodialysis.

These findings suggest that patients with ESRD have a level of dysglycaemia that may not meet the criteria for a diagnosis of diabetes mellitus. This could be due to the repetitive exposure to high glucose concentrations in the dialysate or a true pre-diabetic state[16]. This higher level of HbA1c predicts a higher risk of mortality and cardiovascular disease in patients with ESRD as was demonstrated by Khaw et al and others[7,12] in addition to their increased risk associated with the renal dysfunction[11].

Interference by carbamylated haemoglobin, which is a chemically modified derivative of haemoglobin due to uraemia, can affect the accuracy of HbA1c measurements, as well as genetic variants of haemoglobin (e.g. HbS trait, HbC trait) and elevated foetal haemoglobin (HbF). These may1 interfere with the analysis causing a falsely higher HbA1c[1].

On the other hand, some factors may affect the interpretation of HbA1c results. Any condition that shortens erythrocyte survival or decreases mean erythrocyte age (e.g., recovery from acute blood loss, haemolytic anaemia) will falsely lower HbA1c test results regardless of the assay method used. The role of renal anaemia, erythropoietin intake, and other factors in chronic renal failure is more difficult to evaluate. Recent reports suggest HbA1c underestimates glycaemic control in diabetic patients on dialysis and that glycated albumin is a more accurate indicator of glycaemic control1.

Hypoglycaemia associated with renal failure is more common than generally thought of. Drugs like: propranolol, salicylates, and disopyramide are among the most commonly implicated agents. Additional triggering events are: alcohol consumption; sepsis; chronic malnutrition; acute caloric deprivation; concomitant liver disease; congestive heart failure; and an associated endocrine deficiency. When no obvious cause can be demonstrated, the hypoglycaemia is referred to as spontaneous. Spontaneous uremic hypoglycaemia has been attributed to deficiency of precursors of gluconeogenesis, that is: alanine- deficient gluconeogenesis: impaired glycogenolysis; diminished renal gluconeogenesis and impaired

renal insulin degradation and clearance; poor nutrition; and, in a few cases, deficiency in an immediate counter-regulatory hormone such as catecholamine and glucagon[18]. All of these factors make HbA1c unsuitable for monitoring of glycaemia in ESRD patients and so search for a more robust indicator is required.

The mean HbA1c concentration in controls is different in this study than the 5.45% mentioned in the literature[14] which emphasizes the need to establish a reference value for Sudanese individuals.

A significant positive correlation was found between the duration of the ESRD and the HbA1c concentration. A similar correlation between cholesterol concentration and HbA1c was also found on top of the significantly higher cholesterol in the study group. Both HbA1c and cholesterol are associated with the development of coronary artery disease and, as patients with ESRD are at an increased risk of developing CVD[7,14], HbA1c can play a role in risk stratification and early identification of non-diabetic patients with ESRD at high risk of developing CVD[12,18]. Moreover, a higher HbA1c level is also associated with an increased relative risk of death from any cause other than CVD[10], underscoring its importance in the follow-up of patients.

No correlation was found between the cholesterol level and the duration of haemodialysis, unlike the published findings which showed a positive correlation[17].This could be due to the relatively small sample size, though it again stresses the need to establish local reference values.

Conclusion

This study has shown that patients with ESRD have a higher HbA1c and cholesterol concentration than controls. A positive and significant correlation between the duration of ESRD and the HbA1c concentration and between HbA1c and cholesterol concentration was noticed.

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Comparison between 70% aquaethanolic cinnamon extract effect and glimepiride on blood glucose levels among alloxan-induced diabetic rats

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Abstract:

Background: Diabetes mellitus is a chronic, metabolic disorder characterized by elevated levels of blood glucose which leads over time to serious damages to the heart, blood vessels, eyes, kidneys and nerves. The most common is type 2 which occurs when the body becomes resistant to insulin or cannot produce enough insulin (1). Cinnamon (Girffa) extract is known to reduce postprandial glycemia by stimulating insulin action to uptake glucose by the cells.

Methodology: It was an experimental study performed on 20 albino rats weigting 150 to 200 gms. On 15 of them diabetes was induced using alloxan .After fasting for 8 hours, basal blood glucose was measured and all rats were given standard meal and then the effect of 250mg/kg, 500mg/kg of 70% aquaethanolic extract of cinnamon on blood glucose level one and two hours thereafter was compared with the effect of glimiperide.

Results: Cinnamon aquaethanolic extract in a dose of 250mg/kg reduced glucose concentration significantly (p=0.043) by 25% after one hour and by 11% after two hours. When a dose of 500mg/kg was given, the glucose level was reduced by 19% and 11% after one and two hours respectively (p=0.002, and 0.005). No adverse effect was noticed. Cinnamon extract was as effective as glimiperide.

Conclusion: These findings suggest that cinnamon extract may be used as a natural postprandial hypoglycemic agent.

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Introduction

Diabetes mellitus is a metabolic disorder that affects metabolism of glucose leading to elevated blood glucose. There are 2 types: type 1 also called insulin-dependent diabetes mellitus and this is because the body cannot produce insulin; and type 2 also called non- insulin dependent diabetes mellitus or insulin-resistant, where insulin is present but the body cells are resistant to its action(1). Postprandial hyperglycemia control has been a challenge that faces patients with type 2 diabetes. Cardiovascular disease, one of the major complications of diabetes, is largely influenced by glycemic measures(2). Cinnamon(girffa) has become a natural product of interest because it has been hypothesized to provide health benefits, such as its ability to lower blood glucose. It has been suggested that the modality by which cinnamon exerts its effect on blood glucose can be attributed to its active component cinnamaldehyde (3).

The hypoglycemic effects of cinnnamaldehyde have been investigated before and were thought to be due to promoting insulin release; enhancing insulin sensitivity; increasing insulin disposal; and exerting activity in the regulation of protein-tyrosine phosphatase 1B (PTP1B) and insulin receptor kinase(4-6).

Materials and Methods:

This study was done in Alahfad University for Women-Omdurman, between January 2016 and April 2016. The study included 20 albino rats weighing 150-200gms, five of them were used as control and fifteen were the diabetic (study group). Diabetes was induced using alloxan.

Cinnamon Extract : Cinnamon extract tested in this study was prepared as 70% aquaethanolic extraction. The method of extraction was (macerator method[7]: 100gms of dried cinnamon powder were added to 2 liters of 70% ethanol and kept overnight, then the mixture was filtered to remove solid large particles using Buchner flask and vacuum pump (Buchner apparatus). The suspension was evaporated to obtain concentrated extract, then dried in the hot oven at 80°C.

In vivo inhibition of pancreatic insulin: inhibition of insulin production was induced by introducing alloxan (from Labal Chemi- India). Alloxan is a chemical powder that causes partial destruction of B-cells in the pancreas causing hyperglycemia to the rats. The dose given to the rats was 130mg/kg of rat dissolved in 10ml normal saline. The rats were made to fast for 18 hours. Baseline blood samples were drawn and then alloxan was injected into the back of the neck and then the rats ate their libtium. After 72 hours they were tested for fasting blood glucose to show hyperglycemia which was defined as blood glucose more than 200 mg/dl.

All blood samples were taken from their eyes after anesthesia by chloroform wet cotton. The samples

were collected into fluoride oxalate anticoagulated vacutainers .

The trial: the study was performed on 3 groups of diabetic rats. Group 1: Five diabetic rats were treated with glimepiride (5mg tabs) in a dose of 20mg/kg.

Group 2: Five diabetic rats were treated with cinnamon extract of conc. 250 mg/kg.

Group 3: Five diabetic rats were treated with cinnamon extract of conc. 500 mg/kg.

All rats were made to fast for 8 hours and blood samples were collected at zero time (before giving the medication) and at one and two hours postprandial. The meal was composed of:sorghum, sugar, salt and water, and medications were given by a feeding tube.

Results:

Twenty rats were included in this study. The mean fasting blood glucose in all rats before induction of diabetes was 79mg/dl.

Table I shows the mean concentration of blood glucose in the study group at fasting, one and two hours after giving the medication. There was no significant difference between the effect of glimepiride and cinnamon extract. Secondly, the cinnamon extract on a dose of 250mg/kg showed a rapid effect and similar to a dose of 500mg/kg.

The dose response to cinnamon extract for the first hour postprandial showed rapid decrease in blood glucose of 23% (P.=0.043), and 19.5%, (P=0.002) in doses 250mg/kg and 500mg/kg respectively, and a decrease of 11% (P=0.242) and 8% (p.=0.005) in same doses after 2hours. Whereas the glimepiride group showed a decrease of 13.9% (p=0.62) in the first hour and 17% (p=0.024) in the second hour.

Table I. shows the mean concentration and percentage decrease of blood glucose in the study groups at baseline, one, and two hours after giving medication.

Group	Fasting	Blood glucose conc. and % decrease after 1hr	Blood glucose conc. and % decrease after 2hr	p.value
1/ 250 mg/kg	262mg/dl	202mg/dl 23%	233mg/dl 11%	1hr: p=0.043 2hr: p=0.242
2/ 500 mg /kg	223mg/dl	180mg/dl 19%	250mg/dl 8%	1hr: p=0.002 2hr: p=0.005
3/ Glimepiride 20mg /kg	228mg/dl	196mg/dl 13.9%	189mg/dl 17%	1hr: p=0.062 2hr: p=0.024

Discussion:

Our study showed that alloxan induces hyperglycemia in rats as we compared blood glucose before (mean=79mg/dl) and after (mean=234mg/dl) alloxan induction which was statistically significant.

Cinnamon extract in a dose of 250mg/kg showed significant reduction in blood glucose by 23% (p=0.024) after one hour and by 11% after two hours. So the peak action occured after one hour and its action is relatively short-lived.

After using of 500mg/kg cinnamon extract, blood glucose dropped after 1hour by 19% (p.=0.002) and by 8% after 2hours (p.=0.005) and both were statistically significant. So though cinnamon in a dose of 500 mg/kg reduced blood glucose, its effect was not more profoundly significant than a lower dose of 250mg/kg.

When comparing the effect of 250mg/kg and 500mg/kg of cinnamon extract with the effect of glimepride, the effect was not statistically significant (p=0.637).

Similar reduction in blood glucose level using extracts of cinnamon were shown by other workers who suggested various mechanisms for this effect including enhancement of insulin secretion by beta cells of the pancreas,; reduction of glycemic response to starch in normal rats by inhibiting pancreatic α amylase digestion[1,6].

Conclusion:

This study showed that aquaethanolic cinnamon extract in a dose of 250mg/kg and 500mg/kg could reduce 1hour and 2hours postprandial glucose level in rats, comparable to the effect of oral hypoglycemic drug glimepiride. However, increasing the dose to 500mg/kg did not increase its effect.

Acknowledgment:

We would like to thank Dr Adil Naser Shafee and Alahfad University School of Pharmacy staff for their great help in this trial.

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Case report

Ataxia telangiectasia

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Ahfad University for Women, School of Medicine, Unit of Paediatrics, Mohamed Elamin Hamid Hospital for Children, Omdurman

Abstract:

We report a rare case of a seven- years- old boy from Kosti who presented with progressive ataxia since the age of three. Two years later he developed conjunctival telangiectasia .Examination revealed occulo-motor apraxia. A diagnosis of ataxia telangiectasia was made on clinical findings; low immunoglobulins; high alpha fetoprotein levels and cerebellar atrophy on cranial's MRI. A coordinated multidisciplinary healthcare with follow- up was offered and intravenous immunoglobulin was given on a monthly basis

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Case report:

A seven- years- old Sudanese boy, offspring of a consanguinous marriage, presented to Mohammed Elamin Hamid Teaching Hospital in Omdurman, Sudan, complaining of unsteadiness over the last 4 years. His mother first noticed that her child started to sway backwards and from side to side after he was walking normally at a normal age.

There was past history of recurrent chest infections for which he was admitted many times since the age of 5 months. The condition progressed till he became unable to walk alone .At the age of 5 years his mother noticed abnormal eye movements and reddish discoloration. His previous care has been somewhat fragmented in place. He is the youngest of 4 siblings with no similar condition in the family. His parents were first degree cousins. He did not attend school yet.

Physical examination showed that he is stunted with weight, height and head circumference all below third percentile, his temperature was 37.5º C, blood pressure 90/60 mm/hg and pulse rate was 95/ min and regular.

Eye examination revealed bilateral bulbar conjunctival telangiectasia(figure 1). There were horizontal and vertical nystagmus with normal visual acuity, papillary response and fundi in addition to the presence of normal convergence ability. There were lymph nodes enlargement, skin rash, telangiectasia, hypo- or hyperpgimented areas. Auscultation of the chest showed crackles all over, and the abdomen examination showed no organomegaly.

Neurological assessment showed normal higher mental functions apart from slurred speech and occulo-motor apraxia (difficulty in moving the eye horizontally and he had to turn his head to follow objects) .Limbs examination revealed: hypotonia ; reduced power of grade 4.The deep tendon reflexes were diminished, with difficulties in coordination including intention tremor and disdiadochokinesia. All sensations were intact. Romberg's sign was negative, and the planters were down going. His gait was ataxic .No abnormal movement or skeletal deformities.

His complete blood count, renal function test, liver function test and blood glucose were normal.

Alpha-fetoprotein level was high=130 IU/ml (n<5.8)

Serum immunoglobin assay;

IgA 45.3mg/dl (83-406) - IgG 516mg/dl (700-1600)

IgM 292mg/dl (40-230) - IgE 2.5mg/dl (60-155)

Cranial MRI showed cerebellar atrophy(figure 2).

The chest infections were treated with appropriate antibiotics with good response. Following

consultation with our clinical immunologist, intravenous immunoglobulins were given on monthly bases. He received 0.3-0.4 mg/kg body weight by slow intravenous infusion. A coordinated multidisciplinary health care effort was offered including speech therapy, physiotherapy and psychological support.

Discussion:

Ataxia telangiectasia is a rare neurodegenerative autosomal recessive disease causing severe disability[1]. In 1941 Madame Louis Bar described progressive cerebellar ataxia and cutaneous telangiectasia in a Belgian child[2], and subsequently the disease received her name. Boder and Sedgwick reported seven more cases in 1957[3]. Ataxia telangiectasia can also be classified among neuro-cutaneous syndromes; immunodeficiency disorders; cancer- prone genetic disorders; chromosomal instability syndromes; and abnormal radiosensitivity and DNA repair /processing defects.

Ataxia telangiectasia is caused by a defect in ATM (ataxia telangectasia mutated gene) located on chromosome 11(11q22-23) which prevents broken DNA repair thus increasing the risk of cancer [4].

The incidence worldwide is between 1 in 40.000-100.000 people[2,5] and this indicates its rarity and may explain the delay in diagnosis .All races are affected equally without predilection for gender [2,5].

The presentation of our case is typical[1]; AT presents with progressive cerebellar ataxia in early childhood, telangectasia of bulbar conjunctivae and skin, frequent sino-pulmonary infections, slurred speech and retardation of somatic growth. Intelligence is essentially normal. Examination showed and ataxic child with telangiectasia; hypotonic ; areflexia ; intact sensation and negative Romberg's sign; as seen in our patient; while choreoathetosis are seen more in adults.

The immunoglobulin level and alpha fetoprotein [8] guided us to a firmer diagnosis. About two thirds of cases of AT have abnormalities in the immune system ,the most common: low levels of (IgG, IgA, IgE); not making antibodies in response to vaccine or infection; low number of lymphocytes[6]. Elevated IgM occurs in 60% of cases[7]. On the other hand, approximately 95% of people with AT have elevated level of serum alpha fetoprotein by the age of two which increases slowly over time [8].

According to Tavani et al cerebellar atrophy is found on MRI brain with age starting from early childhood[9]. The diagnosis can be confirmed in the laboratory by finding an absence or deficiency of ATM protein in cultured blood cells[10,11] ; an absence or deficiency of ATM function (kinase assay); and mutation of both copies of the cells ATM gene. These more specialized tests are not always needed, but are particularly helpful if a child's symptoms are atypical.

The delay in making the diagnosis in our case may be attributed to many factors: the rarity of the disease; delayed appearance of telangiectasia; and the previous medical care that had been fragmented in place with no proper follow- up to detect the appearance of new signs timely.

The risk of an AT patient developing any cancer is 37-fold higher than individuals in the general population. The risk of developing lymphoid tumors, however, the most frequently diagnosed cancer in AT patients, is 100-fold higher than in the general population. AT patients have about a 10% risk of developing lymphoma or leukemia. Cancers also occur in the stomach; brain ; ovary; skin; liver; larynx; parotid gland; and breast[12].

There is no treatment known to slow or stop the progression of the neurologic problems. It is only symptomatic and supportive. Multidisciplinary medical team including the neurologist, immunologist, pulmonologist and physical therapist are capable of dealing with many needs in this disease. Prompt treatment of infections, if any, and in some cases, prophylactic antibiotics and immunoglobulin therapy, may be of benefit. Avoidance of X- ray whenever possible. Regular follow- up for early cancer detection is necessary as well as education, socialization and special help in school.

The prognosis is very poor and they usually require wheel chair by 10-11 years. Most patients may not survive beyond their twenties according to the National Cancer Institute. Causes of death are chronic lung disease and lympho-reticular (leukemia and lymphoma) cancers [13].

In conclusion: awareness about this condition and its significant morbidities will help early diagnosis and institution of appropriate supportive treatment.

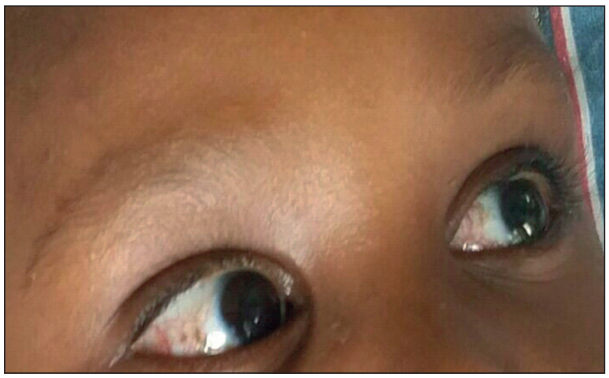

Figure 1. bilateral bulbar telangiectasia

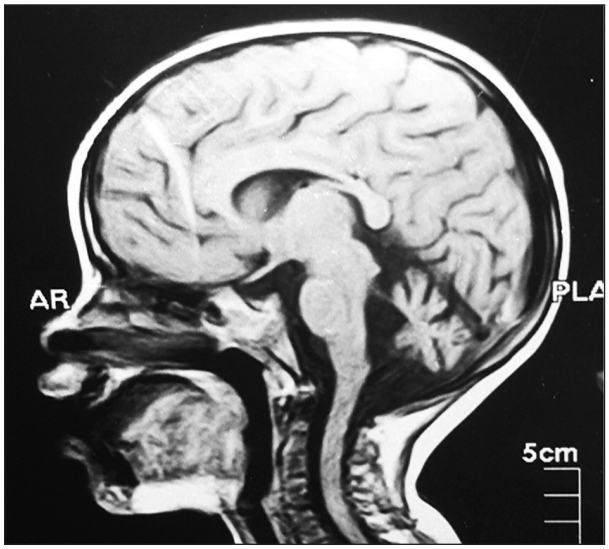

Figure 2. Cranial MRI showing cerebellar atrophy

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Case Repot

Crossed Testicular Ectopia

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Summary

Crossed testicular ectopia (CTE) is an extremely rare congenital anomaly, in which both testes migrate towards the same hemiscrotum through the same inguinal canal. Herein we report a case of a crossed testicular ectopia in a 6- month-old boy. The diagnosis was suggested clinically and supported by ultrasound findings. On groin exploration, both testes were found in the right inguinal canal each one had its own vas deferens and vascular pedicle. A trans-septal orchiopexy was performed by advancing the left testis via the midline scrotal septum into the left subdarots pouch. Literature was reviewed, and mechanisms that are postulated for this anomaly are presented.

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Introduction:

Crossed testicular ectopia (CTE) or transverse testicular ectopia (TTE), is a rare congenital anomaly in which both testes migrate towards the same hemiscrotum via the same inguinal canal[1,2]. A few cases have been reported in the English medical literature (about 147 cases) since the first description by Von Lenhossek[3,4]. Many mechanisms have been postulated for this extremely rare gonadal anomaly[5-7]. However, the exact cause is still poorly understood[1]. Because of the rarity of this clinical occurrence; a definitive diagnosis can't be made preoperatively in most of the cases and the condition is usually encountered intra-operatively during groin exploration for an indirect inguinal hernia or undescended testis with an empty contralateral hemi-scrotum. We present a case of crossed testicular ectopia (CTE) in a 6-month-old boy who was brought by his parents with a left empty scrotum and a right groin swelling. Examination revealed an empty left hemiscrotum and two rounded, soft and mobile inguinal swellings which were consistent with testes in the right inguinal canal. A presumptive diagnosis of CTE was made and supported with ultrasound findings. Operative findings confirmed the diagnosis. He underwent a trans-septal orchidopexy. We reviewed the literature and described various mechanisms that are postulated for this anomaly.

Case presentation:

A 6- month- old Sudanese male was brought by his parents to the Pediatric Surgery Unit at Soba University Hospital because they noticed that he had a left empty scrotum and a right groin swelling during bathing. He was a product of a normal vaginal delivery at a rural hospital where there was no routine neonatal examination performed for him. He passed through normal milestones up to presentation time. Past medical history was significantly unremarkable. There was no history of undescended testis in the family.

On general examination, he was a well- looking boy with both weight and height within normal centiles according to his age and sex. The left hemiscrotum was well- developed but empty and no testis was palpable in the left inguinal canal. There were no other palpable swellings in the left lower abdomen, root of penis or the left upper medial thigh. Right groin examination revealed two separate, small (2X4 cm), rounded, soft and mobile inguinal swellings over the superficial inguinal ring with a testicular texture. Additionally,

a normally thickened spermatic cord was felt easily in the right groin. The findings were very consistent with a right palpable undescended testis (UDT) and a left crossed ectopic testis (CET). No cough impulses were noticed over both groins. A distal coronal hypospadias was also noticed. Systemic examination was essentially normal. A presumptive diagnosis of a crossed testicular ectopia with coronal hypospadias was made.

Ultrasound (US) examination revealed an empty left hemi-scrotum with no testis-like shadow in the left inguinal canal or intra-abdominally. No Mullerian duct remnants were seen in the left side. Right groin US showed two testes-like shadows in the right inguinal canal. No indirect inguinal hernias were seen in both sides. The child was booked for an elective trans-septal orchiodopexy after appropriate preoperative investigations.

He underwent right groin exploration under general anesthesia. A right inguinal incision was made and the right inguinal canal was opened. The right spermatic cord was delivered out and two, viable and normally-sized testes were found. Both testes had a (common) meso-orchium proximally, but each one had a separate vasa deferenes and its own vascular pedicle (Figure 1). They were almost equal in size. There was no associated right-sided indirect inguinal hernia. No Mullerian duct tissue remnants were found.A meticulous dissection was done to separate the two testicular tissues with preservation of their vasa deferentia and vascular pedicles. The right testis was fixed into the right subdarots pouch with Vicryl 5/0, while the left one was advanced through the midline trans-septum into the left subdarots pouch, under no tension, as the length of the left spermatic cord was fortunately enough to be advanced (Figure 2). The latter was fixed into the left subdarots pouch with Vicryl 5/0. The postoperative recovery was uneventful and the operative findings were explained to the parents.

Discussion:

Crossed testicular ectopia (CTE) is a rare gonadal anomaly in which both testes migrate towards the same hemi-scrotum via the same inguinal canal [1,2] It is considered as one of the rarest types of testicular ectopia[8]. The crossed ectopic testis can be found at different locations including contralateral hemi-scrotum, contralateral inguinal canal (as in the current case) and contralateral femoral triangle[9]. It usually occurs in the right side (as in the present case), however, left sided cases were also reported[10].

Several theories have been postulated to explain embryological basis of this anomaly[5- 7]; most of them were linked to the abnormalities of normal testicular descent with a special emphasis on the role of gubernaculum[11]. Berg had suggested that both testes arose from the same genital ridge[5]. In the same context, Gupta and Das[6] postulated that adherence and fusion of the developing Wolffian ducts takes place early on and that descent of one testis causes the other one to follow it toward the same hemiscrotum[6]. However, Gray and Skandalakis[7] suggested that each testis is arising from the ipsilateral genital ridge and the crossing-over occurs during testicular descent. This theory is supported by the observation that, in most of the cases, each testis has its own vas deferent and vascular pedicle[7]. Nevertheless, the exact mechanism is still unknown[1].

The condition is associated with a wide variety of congenital anomalies. Accordingly, a classification system has been proposed in the literature[12] and it was based on the type of the associated anomalies[12]. Type I is the most common type (40-50%) and it is associated with indirect inguinal hernia; Type II (30%) is associated with persistent Mullerian duct tissues; and Type III (20%) is associated with hypospadias, pseudo-hermaphroditism or scrotal anomalies[12]. Our reported case belongs to the latter type as it was associated with a distal coronal hypospadias.

Most cases of CTE are encountered incidentally during groin exploration for undescended testes or repair of indirect inguinal hernias with an empty contralateral hemiscrotum[10,13]. The clinical presentation is generally with unilateral (or bilateral)

cryptorchidism or indirect inguinal hernia in the vast majority of cases[13]. A very rare presentation with an incarcerated irreducible indirect inguinal hernia was reported in the literature[14]. Nevertheless, the diagnosis can be barely established on clinical examination alone as there is always a wide range of differential diagnoses that include: testicular duplication; hydrocele of the cord; spermatocele ; Morgagni cyst; and possibly testicular tumors[15].

Ultra-sonography is a good initial diagnostic investigation that can be used to assess the condition[15]; however, MRI is more superior in delineating the anatomy for preoperative localization of the testes and detection of Mullerian tissue remnants (if they are present), but it is rarely used[15]. Laparoscopic search is considered the gold standard for both diagnosis and management of this condition[16].

The aim of the surgical management of CTE is fixation of testes into the scrotum and to search for Mullerian duct remnants[15]. In addition, long-term follow up is advised by many authors due to the increased risk of associated testicular cancers[10] as testicular malignancy has been reported in some cases, especially when cryptorchidism was an association[15]. A variety of procedures have been described, including a staged- surgery to bring the ectopic testis into its correct canal, trans-septal orchidopexy and extra-peritoneal transposition[15].

In conclusion, crossed testicular ectopia is an extremely rare anomaly that is encountered during the surgical exploration for an indirect inguinal hernia or undescended testis with an empty contralateral hemiscrotum. Various associated anomalies have been reported and a classification system is established based on the type of these associated anomalies. Trans-septal orchidopexy is a common approach for the management of this condition while the laparoscopic search is the gold standard for both diagnosis as well as management.

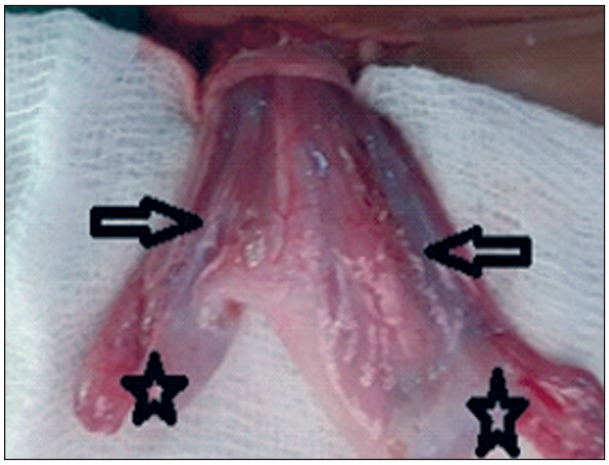

Figure 1. The right spermatic cord delivered out with two testes (stars) and their vas deferenti and vascular pedicles (horizental arrows).

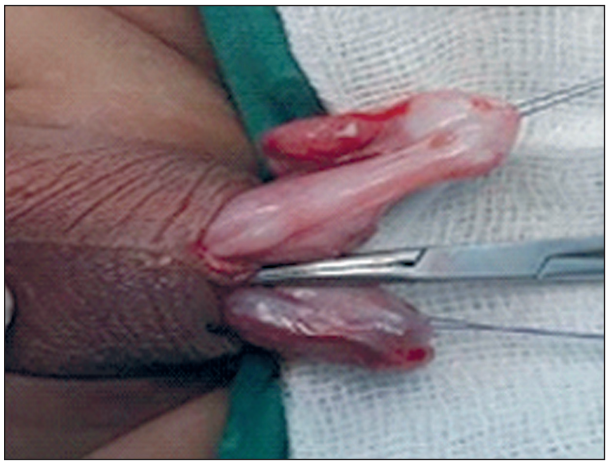

Figure 2. Showing fixation of both testes into their corrsponding subdarots pocuhes with advancement of the left one throught the midline scrotal septum.

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- The justification of an internationally accepted style of reference citation can be summarized as follows:-
- Correct and complete referencing of scientific and medical publications is an essential component of the 'scientific method' when recording the outcome of research.
- To facilitate formatting scientific papers for more efficient peer reviews and publications.
- An unambiguous system of referencing allows other researchers and reviewers of manuscripts to access the cited literature to validate claims and arguments.
- To successfully secure research funding, the research proposal including the existing literature on which it is based should be convincing and easily accessed by reviewers.
- Uniform and complete citation formats facilitates quotation and reference compilation for researchers and postgraduate students.

The following is a summary to supplement the Instructions to Authors for referencing of manuscripts submitted to KMJ. It is based on the Vancouver Style and is the preferred referencing format for writing of dissertations, theses and other referenced writing in the Faculty of Medicine, University of Khartoum:-

1. References should be numbered consecutively throughout the text in the order in which they appear.
2. No references should be included in the abstract.
3. Identify references in the text, tables and legends by numerals in parenthesis e.g. (1), (2,3) or (3-6).
4. When citing authors in the text, acknowledge only the first author where there are three or more authors, e.g. Smith et al (1998) stated that ….(1).
5. Where there are two authors cite both, e.g. Adam and Ehsan (2003) reported that ….(2). Note that numerals in parenthesis at the end of a sentence are written before the full stop.
6. The list of references should begin on a new page and given the numbers which indicate order of citation.
7. All authors should appear in the list of references i.e. all references are listed in full.
8. Where more than 6 authors are registered, write the first 3 authors followed by et al.
9. The order of author/s initials, punctuation, title of article, year, journal title – in accepted abbreviated form, volume and page numbers, constitute a full reference citation. The following

are examples of commonly used reference sources:

Reference in journals

General format including punctuation,

Author/s, title of article, title of journal (in italics with no full stops), year; volume number: page numbers.

e.g. Rose ME, Huerbin MB, Melick J, JK et al. Regulation of interstitial excitatory amino acid concentrations after cortical contusion injury. Brain Res 2002; 935: 40-6.

References in books

Author(s) of a book

General format including punctuation.

Author(s) Title: sub-title. Edition. Place of publication: Publisher; Year

e.g. Guyton AC, Hall JE. Textbook of Medical Physiology. 10th Ed. Philadelphia: Saunders; 1990.

Author(s) of a chapter in a book

General format including punctuation

Author(s) of the chapter. Title: sub-title of chapter. In: Author(s) (or editors) of the book. Title: sub-title of book. Place of publication: Publisher; Year; page numbers.

Elmunshid HA. Special senses. In: Sukkar MY, Elmunshid HA, Ardawi MS, editors. Concise Human Physiology 2nd Edn. Oxford: Blackwell Science; 2000.p.401-23.

Reference on-line

Example (from The Michener Institute for Applied Health Sciences, Learning Resource Centre: Irc@ michenere.ca).

Book on the Internet

Foley KM, Gelband H, editors. Improving palliative care for cancer [monograph on the Internet]. Washington: National Academy Press; 2001 [cited 2002 Jul 9]. Available from: http://www.nap.edu/books/o309074029/html/.

Internet homepage/website

Cancer-Pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources, Inc.; c2000-01 [updated 2002 May 16; cited 2002 Jul 9]. Available from: http://www.cancer-pain.org.

For a fuller range of examples of citation from other sources of references, there are innumerable sites on the internet. Please also consult the publications cited in KMJ instructions to authors and the references cited below:-

1. Uniform requirements for manuscripts submitted to biomedical journals: writing and editing for biomedical publication [home-page on the Internet]. Philadelphia, PA: International Committee of Medical Journal Editors; [updated 2003 Nov; cited 2004 Oct 9]. Available from: http://www.icmje.org/.
2. Style manual for authors, editors and printers. 6th Ed. Milton, Qld: John Wiley & Sons; 2002