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Serum Neuron Specific Enolase use in Detecting Brain Injury in Children with Congenital Heart Disease before Undergoing Cardiac Surgery

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Abstract

Background: Many children with Congenital Heart Disease (CHD) suffer from neurological derangements, whether clinically evident or subtle. Brain injury may be pre-existing before surgery, making them at increased risk of adverse perioperative neurological outcomes. Serum Neuron-Specific Enolase (sNSE) is a well appreciated marker for neuronal damage that has been demonstrated to detect perioperative brain affection in children with CHD.

Aim of the study: The study aimed to utilize sNSE to detect presence of brain injury in children with CHD prior to performing cardiac surgery.

Methods: The study included 85 children divided into two groups; Group I included 45 patients with CHD while Group II (control) included 40 healthy children of the same age group. Patients were included if they had clinical and echocardiographic documentation of CHD. Children with pre-existing neurological disorders or previous surgery were excluded. Blood samples were withdrawn from every participant to measure sNSE.

Results: sNSE level was significantly higher in Group I than Group II, with a mean value of 6.90 ± 6.94 and 3.79 ± 2.26, respectively (p-value 0.008). No significant correlation was found between sNSE levels and age, body mass index, or sex. There was no significant difference between cyanotic and acyanotic CHD patients.

Conclusion: sNSE measurement demonstrated the presence of a significantly higher incidence of baseline brain damage in CHD patients compared to normal subjects, before undergoing any interventions. sNSE could be further investigated as a risk stratifying tool to label children at risk of developing adverse neurological outcomes after surgery.

Keywords: Congenital heart disease; Neurological damage; Serum neuron-specific enolase; Perioperative brain injury

Introduction

Congenital Heart Disease (CHD) has been shown to adversely influence the neuro-developmental outcome of children in many ways. Neurological complications contribute significantly to mortality and morbidity from CHD with serious long-term consequences [1]. Up to 50% of children with CHD experience neurodevelopmental and behavioral problems including hypotonia, hypertonia, seizures, cognitive impairment, delays in speech, language, visual-motor and visual-spatial skills, attention deficit/hyperactivity disorder and learning disabilities [2]. However, the neurodevelopmental impact CHD leaves on these patients is not always clinically detected. Many children were found to be clinically free from the above findings and yet had cranial ultrasound, MRI and or EEG findings supporting neurological affection [3-5]. Recent advances in medical management, trans-cutaneous catheter intervention, surgical procedures and cardiopulmonary bypass, have significantly increased the survival rate of such children. However, despite these advances, there still remains a well-recognized incidence of associated procedural complications [2]. One of the serious and well known complications in infants undergoing cardiac surgery for CHD is cerebral damage.

Evidence that neonates and infants with CHD are at increased risk of adverse neurological outcomes after surgery does exist [6], and the presence of preexisting neurological problems preoperatively shares in increasing this risk [7]. It has for long been debated whether the resultant neurological complications arising in children after surgery were due to the impact of surgery alone or due to a predisposition to neurological affection due to CHD in the first place [8]. The presence of preexisting central nervous system disorders in patients with congenital heart disease has been found to be multifactorial and has been related to either a congenital central nervous system malformation or an adverse neurological event preoperatively [9,10]. The developing fetus with congenital heart defects may be exposed to hypoxia and abnormal cerebral perfusion in utero and these insults on the brain may continue during the neonatal period as a result of the failing heart [11]. It is thus crucial to risk stratify CHD patients before surgery to detect those with pre-existing subtle neurological derangements not clinically detected. This would be useful in parent counseling, early diagnosis and rehabilitation therapy, and would aid in developing therapeutic strategies to minimize patients' exposure to surgical stresses that may complicate their situation and lead to further cerebral damage [12]. Radiological techniques in the form of cranial ultrasound, MRI, MRS, Near Infra-red spectroscopy, electroencephalography and inflammatory and immunologic markers have been previously advocated in the process, but many of those are time-consuming, expensive, technically demanding and not always readily available [13]. The use of serum brain markers for diagnosis of neuronal injury has long been implicated in early detection of brain injury. Neuron-Specific Enolase (NSE) is a human γ enolase and is one of the appreciated biomarkers used to detect neuronal tissue damage [14]. Since NSE cannot be secreted by cells, an increase of NSE in Cerebrospinal Fluid (CSF) or serum is a marker for neuronal damage [15]. It had been used for detection of hypoxic ischemic encephalopathy in cases of perinatal asphyxia for the application of

neuroprotective strategies [16]. It has also been used in studies to predict neurological outcome peri-operatively in children undergoing cardio-pulmonary bypass and cardiac catheterization [17]. While previous researchers have focused on the postoperative period in their investigation of brain vulnerability, the pattern of preoperative background of neurological status has not been well reported in this population of children suffering from congenital heart disease. It is believed that the presence of comorbidity and vulnerability of these infants makes this an important timeframe to study [18]. The aim of this study was thus to utilize serum Neuron-Specific Enolase (sNSE) to detect the presence of brain injury in infants and toddlers with congenital heart disease prior to performing surgery.

Aim of the study

The study aimed to utilize serum Neuron-Specific Enolase (sNSE) to detect the presence of brain injury in infants and toddlers with Congenital Heart Disease (CHD) prior to performing cardiac surgery.

Methods

We conducted a case control study, in National Heart Institute and El Fayoum University hospital from October 2018 to February 2019, including 85 Egyptian children. Group I (cases group) included 45 children with CHD (31 males and 14 females). An age and facility matched control group (group II) was randomly selected and included 40 healthy children without CHD (32 males and 8 females). This study has been reviewed by the Faculty of Medicine Research Ethical Committee. The researcher informed the participants about the objectives of the study, the examination, investigation that have been done. Also, the confidentiality of their information was respected and their right not to participate in the study was ensured. Cases of CHD and disease free controls were aged from 2 months to 3 years and were from both genders. Cases were ascertained through follow up hospital records. The inclusion criteria for CHD were: (1) Documented clinical presentation consistent with CHD such as cyanosis, recurrent chest infections, coupled with presence of cardiac murmur; (2) Echocardiographic data showing presence of CHD. Disease free controls were defined as participants without clinical or echocardiographic evidence of CHD disorders or other co-morbidities (Table 1).

Demographic Data				
	Group I: patients (n=45)	**Group II: healthy controls (n=40)**	**t/x2#**	**p-value**
Age (months)				
Mean ± SD	15.43 ± 10.39	25.30 ± 9.86	4.45	<0.001**
Range	2.0-36.0	6.0-36.0		
Gender				
Female	14 (31.1%)	8 (20%)	1.363#	0.243
Male	31 (68.9%)	32 (80%)		

Table 1: Demographic data, age, gender.

Patients with known CHD who had undergone cardiac surgeries or cardiac interventions were excluded along with patients with pre-existing neurological disorders such as seizures, traumatic brain injury, encephalitis, stroke, neuromuscular conditions, neuro-metabolic diseases, hereditary diseases such as tuberous sclerosis, syndromic disorders, etc. Patients were also excluded if they were known to suffer from neuroendocrine tumors e.g. neuroblastoma, retinoblastoma, known hemolytic anemias, hepatic failure, or end stage renal failure; all such diseases were found to raise sNSE levels, independent from brain injury, resulting in false positive results. In addition, preterm infants were excluded from the study.All participants were subjected to detailed history and physical examination with special emphasis on history and clinical findings of the cardiac condition, in terms of complaint, duration since discovery, medications received, and complications (if any). Any conditions of medical importance (e.g. convulsions, loss of motor skills, poor social skills) that would hint to a pre-existing neurological condition were looked for to exclude patients with syndromic disorders (Table 2).

Clinical diagnosis of congenital heart disease cases	
Echo findings	**Patients (n=45)**
PAPVD	2 (4.4%)
PDA	6 (13.3%)
TGA	1 (2.2%)
PS	7 (15.6%)
VSD	8 (17.8%)
AR	1 (2.2%)
TOF	14 (31.1%)
ALCAPA	1 (2.2%)
ASD	3 (6.7%)
DORV	4 (8.9%)

Table 2: Clinical diagnosis of congenital heart disease cases.

Participants were subjected to Transthoracic Echocardiography (TTE) that was performed with the patients lying on a standard hospital bed by the use of a GE Vivid 5 and 7 echo machines, using 3 MHz-5 MHz phased transducers. General data was obtained mostly from subcostal, parasternal long and short-axis, and apical four chamber views: Situs, atrioventricular concordance, ventriculoarterial concordance, great artery relations, other anomalies, tricuspid, pulmonary, mitral and aortic valve abnormalities.

Cases were defined according to their anatomic classification. The participants were distributed among the following pathologies: Atrial Septal Defects (ASD); Ventricular Septal Defects (VSD); ventricular septal defect with Aortic Regurgitation (AR); Patent Ductus Arteriosus (PDA); Pulmonary Stenosis (PS); Tetralogy of Fallot (TOF); Partial Anomalous Pulmonary Venous Drainage (PAPVD); Transposition of Great Arteries (TGA); Double Outlet Right Ventricle (DORV); Anomalous Left Coronary Artery from Pulmonary Artery (ALCAPA).

Laboratory investigations performed to all the study population included hemoglobin concentration and serum Neuron Specific Enolase (sNSE). 1 ml blood sample was withdrawn from every participant in an EDTA vacutainer tube for hemoglobin concentration test and a 2 ml blood sample was withdrawn from every participant in a vacutainer tube with gel for serum separation to carry out Neuron Specific Enolase test.

The reagent CanAg NSE EIA Kit was used for the quantitative determination of NSE in human serum. Hemolysed samples were excluded (Table 3).

sNSE Concentration in Group I (patients) and Group II (healthy controls)				
sNSE (µg/l)	**Group I: patients (n=45)**	**Group II: healthy controls (n=40)**	**t-test**	**p-value**
Mean ± SD	6.90 ± 6.94	3.79 ± 2.26	2.703	0.008*
Range	1.13-40.61	1.51-13.04		

Table 3: sNSE concentration in Group I (patients) and Group II (healthy controls).

Statistical analysis

Recorded data was analyzed using the statistical package for social sciences, version 25.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean ± Standard Deviation (SD) and descriptive statistics were used to describe variables. Qualitative data were expressed as frequency and percentage.

The following tests were done: (1) Independent-samples t-test of significance was used when comparing between two means, (2) chi-Square test to test relationships between two variables e.g. while comparing male to female groups.

The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant when p-value <0.05, p-value <0.001 was considered as highly significant. To compare between two different groups, independent samples T-test or corresponding statistical analysis for nonparametric data was used (Figure 1).

A minimum total sample size of 82 samples (a minimum total sample size of 43 is recommended for group 1, and 39 for group 2) would be sufficient to detect the effect size of 0.56 with a power (1-β) of 80% (=0.80) at a significant level of p<0.05.

According to our study, the total sample size of 85 samples represented by 45 samples for group 1 (patients) and 40 samples for group 2 (controls) has a power of 81.1% (=0.811) (Figure 1). The sample size and power of study were calculated according to G*Power software version 3.1.9.4.

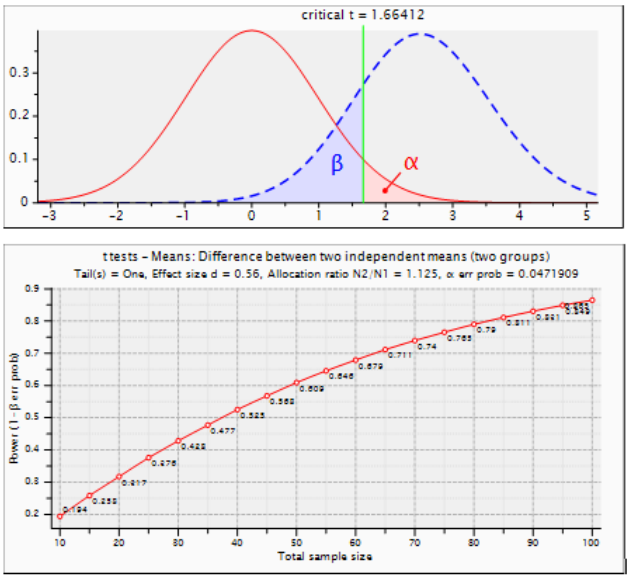

Figure 1: Graphical presentation of α, β, power (1-β) and total sample size.

Results

The study included 85 children. Group I included 45 cases with CHD (31 males and 14 females) and Group II included 40 healthy children (32 males and 8 females) forming the control group. Range of age in all study populations was between 2.0 months-36.0 months, mean age was 15.43 months ± 10.39 months in cases and 25.30 months ± 9.86 months in the control group. 31.1% of the cases were females and 68.9% were males, while 20% of the control groups were females and 80% were males. The mean weight of cases in the study was 8.66 kg ± 2.58 kg, mean height was 73.29 cm ± 11.95 cm and mean BMI was 15.79 kg/m^2 ± 2.04 kg/m^2. The most common echocardiographic finding encountered in the study was TOF (31.1%), followed by VSD (17.8%) and pulmonary stenosis (15.6%). Most of the CHD cases in this study were first and second order among siblings. It was also observed that the subjects with congenital heart disease were mostly descendants from non-consanguineous marriage. The most important finding was that Group I patients showed a higher sNSE concentration than Group II, with a statistically significant difference, p-value 0.008. The Odds ratio of Patient/Control was 3.805. According to this result, patients with CHD were 3.805 times more likely to have increases in their NSE concentration than healthy controls. There was no significant difference between sNSE levels in cases with cyanotic heart disease when compared to sNSE levels in cases with acyanotic heart disease, p-value 0.45 (Table 4).

sNSE concentration in cyanotic and acyanotic heart disease				
NSE Conc (µg/l)	**Cyanotic heart disease group (n=21)**	**Acyanotic heart disease grp (n=24)**	**t-test**	**p-value**
Mean ± SD	6.07 ± 5.67	7.63 ± 7.93	0.748	0.459
Range	1.85-22.42	1.13-40.61		

Table 4: sNSE concentration in cyanotic and acyanotic heart disease.

A correlation did not exist between the sNSE concentration in infants (less than 1 year of age) when compared to its concentration in older subjects, giving a mean of 6.18 ± 5.38 in infants and 7.37 ± 8.27 in older subjects, p-value 0.58 (Table 5).

sNSE concentration in patients aged less than 1 year and others aged more than 1 year				
NSE Conc. (µg/l)	**Less than 1 year**	**More than 1 year**	**t-test**	**p-value**
Mean ± SD	6.18 ± 5.38	7.37 ± 8.27	0.558	0.58
Range	1.86-22.42	1.13-40.61		

Table 5: sNSE concentration in patients aged less than 1 year and others aged more than 1 year

Group I patients with low BMI percentiles (below 5th percentile) showed a lower sNSE concentration with a mean of 4.52 ± 1.81 in comparison to those in the same group with normal percentiles (above the 5th percentile up to 97th percentile), who had a mean of 7.35 ± 7.32. However, this difference was not statistically significant, p-value 0.399 (Table 6).

sNSE concentration in patients according to BMI percentile				
NSE Conc (µg/l)	**Patients with low BMI percentile**	**Patients with normal and high BMI percentile**	**t-test**	**p-value**
Mean ± SD	4.52 ± 1.81	7.35 ± 7.32	0.852	0.399
Range	2.69-6.79	1.86-40.61		

Table 6: sNSE concentration in patients according to BMI percentile.

Discussion

Congenital Heart Disease (CHD) is notorious for its association with neurological derangements, sometimes clinically evident, but, at other times, subtle. Patients with these derangements have a worse prognosis when referred to surgery. It is thus crucial to risk stratify CHD patients before surgery to detect those with pre-existing subtle neurological derangements not clinically detected in order to develop peri-operative prophylactic and therapeutic strategies to minimize their exposure to surgical stresses that may complicate their situation. This could ultimately limit the always feared perioperative cerebral damage [12].

In our study, we tested the utility of sNSE to detect the presence of brain injury in CHD children prior to referral to surgery. Our study included 45 cases of CHD and 45 controls of healthy children sharing the same age group. The sNSE concentrations were significantly higher in the CHD group, denoting a higher incidence of brain injury that was already present, even before the patients were referred to surgery.

In our study, it was found that 60% of the cases were offsprings of non-consanguineous marriage. These results go in contradiction with those of Bassili et al. [19], who mentioned positive consanguinity as a significant factor for developing congenital heart disease. A systematic review of consanguinity in congenital heart disease performed focusing on non-syndromic disease also suggested that the risk for congenital heart disease is increased in consanguineous unions in the studied populations, principally at first cousin level [20]. However, it is fair to mention that in families with history of congenital heart, genetic predisposition becomes a confounder in the relationship between developing CHD and consanguineous marriage. A possible explanation for this dissimilarity between our study and the previous studies may be that we have excluded syndromic cases in our study.

Regarding birth order, we found that around 70% of CHD cases were from lower birth orders, 1st and 2nd. This is, however, against results from Csermely, et al. [21] who confirmed the association of high birth order with the risk of Transposition of the Great Arteries (TGA), Pulmonary Stenosis (PS), and Patent Ductus Arteriosus (PDA).

This study also highlighted that the commonest disease encountered in the cyanotic heart defects cohort was Fallot's tetralogy, while in the acyanotic population, the commonest disease was VSD followed by Pulmonary Stenosis (PS). The Alexandrian study by Bassili et al. [19], also found the commonest cardiac defects to be VSD, PS, and ASD. PS ranked as the second commonest defect, a peculiar finding in our Egyptian population.

In the study by Atwa et al. [22], the most frequent two diseases were ASD (28.8%) and VSD (28.2%). Schwedler et al. [23] published a study performed to assess the frequency and spectrum of congenital heart defects among live births in Germany, where the most common lesions were VSD, ASD and valvular PS with 52.7, 18.3 and 6.6 per 10,000 live births, respectively. A single ventricle, tetralogy of Fallot and complete TGA were the most common "severe" cardiac lesions (3.0, 2.7 and 2.3 per 10,000 live births).

To the contrary, a prospective study performed by Abou-Taleb et al. [24] on 50 neonates admitted to Neonatal Intensive Care Unit (NICU) of Sohag University Hospital, Upper Egypt, found the most common type of cyanotic CHD to be D-transposition of great arteries (D-TGA) (66%) followed by complex CHD (12%) and Hypoplastic Left Heart Syndrome (HLHS) (12%), whereas the least common type was hypoplastic right ventricle (2%). Such conditions were not encountered in our study as such types of CHD are so severe to allow the patient to thrive beyond neonatal age and enter our age group.

The most important finding in our study was the sNSE concentration. A significant difference was noted between the mean levels of sNSE in serum of CHD patients (6.90 ± 6.94) in comparison with healthy subjects (3.79 ± 2.26). After reviewing literature, we found that there were no previous studies dedicated solely to studying the level of markers of brain injury in children with CHD prior to surgery and comparing them to normal controls to eliminate the effect of cardiac surgery as a possible cause behind these brain derangements. Pre-existing brain injury, however, has been indirectly addressed in some previous studies [8,17,25]. Only in these studies and others dealing with the same topic, the focus was mainly to compare pre- and post-cardiac surgery levels of serum neuronal biomarkers to detect peri-operative brain injury. However, in their

discussion of results, some authors postulated about possible pre-existing prenatal brain injury [17].

The study by Trakas et al. [17] found high levels of serum CNS derived proteins in their subjects prior to surgery. They demonstrated that NSE levels which rose following bypass surgery for neonates with CHD decreased to levels significantly lower than the preoperative levels by the seventh postoperative day. They concluded that this drop to below preoperative level was due to preexisting prenatal brain injury that could be enhanced by longer surgical times. This comes in agreement with our study.

On the other hand, our findings are contradicted by those of Simsic et al. [25] and Pironkova et al. [8], who demonstrated that the amount of NSE in patient sera prior to surgery did not differ significantly from that in normal cord blood. The negative correlation between NSE levels and brain structural abnormality scores (which contradicted the anticipated opposite result) is due to the fact that some neonates with complex CHD have a decreased neuronal volume at birth and therefore less volume of neurons capable of cell death leading to generally lower NSE levels (when compared to children without CHD with normal neuronal tissue mass) [17]. Therefore, those with lower peak NSE levels had less neuronal cell volume and were more likely to have ventriculomegaly. This is supported by a number of investigations demonstrating that there are both anatomic and functional neurologic injuries prior to surgery and that total brain volume is decreased in the third trimester as demonstrated by fetal MRI in neonates with CHD [26-28].

Our study also demonstrated no significant impact of body mass index percentile on serum NSE levels. However, a study performed by Hoffmann et al. [29] on adult population to investigate the association between serum NSE levels, Body Mass Index (BMI), total Gray Matter Volume (GMV), and magnetic resonance imaging-based indices of aging, hypothesized that increased serum NSE levels are a result of obesity-associated structural damage of gray matter observed in BMI <25. Hoffmann et al. [29] also reported no significant linear association between NSE and age, the finding which our study conquers with.

Limitations

Our study may be subjected to some limitations, one of which is the non-specificity of NSE. This is due to the presence of NSE in platelets and erythrocytes [30] and hence, even limited hemolysis could substantially increase NSE levels in plasma. NSE is also located in peripheral neuroendocrine cells, which has encouraged studies evaluating its use as a marker of neuroendocrine tumors such as non-small cell lung carcinoma. In our study, 5 samples from the control group were discarded due to hemolysis evident by naked eye. However, some studies implemented the use of spectrometry to exclude cases of covert hemolysis.

The kits used in our study, CanAg NSE EIA, did not provide normal reference ranges of sNSE, so we used matched sNSE results from those of normal controls. Even previous studies studying this subject did not give identical results regarding the “normal” sNSE level in children. According to our controls, the normal reference range was 3.79 ng/ml ± 2.26 ng/ml. A mean value of 7.5 ng/ml ± 2.1 ng/ml was documented in a study by Zeltzer et al. [31] and a mean of 9.09 ng/ml ± 4.38 ng/ml was recorded by Abbasoglu et al. [32] in young infants. Though close, these results are not identical.

In addition, the age in our study ranged from 2 to 36 months, which may be a bit of a wide range. According to the study by Abbasoglu et al. [32], the normal range of NSE differed between preterm newborns, term newborns (less than 1 month old) and young infants (1-3 months old). Although our study did not include preterm or term newborns, we cannot safely postulate that reference values would be the same for younger and older children.

Regarding the patient data, the patients in the case group had different types of CHD, yet did not include the “severe” cyanotic CHD forms (as HLHS, TGA and others) or the complex CHD cases. Such findings might have added to the value of the serum brain injury marker.

Conclusion

We demonstrated that sNSE levels were found to be significantly higher in patients with CHD compared to children without CHD. This shows that there is a higher incidence of baseline brain injury in CHD patients, even before they undergo any surgery or intervention. However, sNSE levels did not differ to a significant level depending on the type of congenital heart defect. Our study supports the preconception that biochemical monitoring of CHD infants at risk for adverse outcomes is becoming possible and sNSE could be used as a risk stratifying tool to label children at risk of developing adverse neurological outcomes after surgery. Further investigations on wider study populations are needed in order to include the serum marker NSE in CHD children daily management.

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