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Original Article

Tyrosine Hydroxylase Expression is Associated with Bone Marrow Infiltration in Neuroblastoma Patients.

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ABSTRACT

Background: Neuroblastoma is a complex heterogeneous disease. Bone marrow is the most commonly affected metastatic site.

The aim of the work: The current study aimed to assess the role of tyrosine hydroxylase in diagnosing bone marrow infiltration in neuroblastoma.

Methods: Tyrosine hydroxylase was assessed in the bone marrow aspirate of 104 pediatric neuroblastoma patients, compared to 25 matched normal controls by real time polymerase chain reaction. The data were correlated to the clinic-pathological features of the patients, response to treatment, bone marrow infiltration, disease free survival and overall survival.

Results: Tyrosine hydroxylase was expressed in 78/104 [75%] of the patients. Bone marrow infiltration was significantly higher in patients with high tyrosine hydroxylase expression compared to those with tyrosine hydroxylase low expression [median [range]: 193 [0-277750] versus 4 [0- 7849]; p=0.003]. Use of tyrosine hydroxylase for diagnosis of bone marrow involvement in neuroblastoma had a sensitivity of 55.2%, a specificity of 65.2%, and positive predictive value of 66.7% and negative predictive value of 53.6%.

Conclusions: Tyrosine hydroxylase may serve as a useful tool for diagnosis of bone marrow infiltration in neuroblastoma. Bone marrow infiltration is associated with poor disease free survival and overall survival.

Keywords: Neuroblastoma; Tyrosine hydroxylase; Bone marrow.

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* Main subject and any subcategories have been classified according to the research topic.

INTRODUCTION

Neuroblastoma [NB] is the most prevalent malignant tumor in infancy [1]. It ranked as the most second extracranial solid malignancy among children, and is responsible for more than 15% of cancer-related deaths in this age group [2, 3].

NB is an embryonic neoplasm that originates from the neural crest stem cells found along the sympathetic neural chain. This neuroendocrine tumor is capable of taking up, storage and secretion of catecholamine metabolites. Diagnosis of NB is usually established on the basis of pathological confirmation and elevated urinary catecholamine levels [2,4]. The clinical course of NB is widely heterogeneous. The tumor may undergo spontaneous regression or may show rapid progression, metastasis and/or resistance to many therapeutic agents. The therapeutic approach and the prognostic outcome of patients are usually guided by many genetic markers including MYCN, anaplastic lymphoma kinase [ALK] and TrkB [5].

The International Neuroblastoma Staging System of NB comprises five stages: 1–4 and 4S. Even with multimodal therapy, patients with metastatic stage 4 tumor are expected to have poor prognosis [6]. In this stage, bone marrow [BM] evaluation is a routine element of clinical staging because BM is a common target of malignant cell infiltration [7, 8].

In spite of the significant progress achieved in our understanding of the biological nature and genetic heterogeneity of NB in the recent decades, treatment outcome remains poor and there is a tremendous need for better diagnostic, prognostic and therapeutic approaches [9, 10]. Catecholamine biosynthesis has an important role in the pathogenesis and progression of NB, and accordingly, regulation of this process is suggested as a novel target for NB management [11]. Tyrosine hydroxylase [TH] serves as an enzyme that limits rates of biosynthesis of catecholamine. Hence, quantitative analysis of TH mRNA in BM and blood was recognized as a reliable marker, both for prognostic evaluation and therapeutic monitoring of NB [12,13]. Interestingly, it was found that adding multiple molecular targets to isolated TH analysis didn't increase its power as a predictive marker of NB prognosis [14].

Detection of BM involvement is performed through many techniques including cytological and histological examination, which have low sensitivity for detection of tumor cells [15]. Other more sensitive technologies include immunocytological investigation of BM slides, flow cytometry and reverse transcriptase PCR [Rt-PCR]. The Rt-PCR is characterized by its high sensitivity, reproducibility, in addition to its cost-effectiveness [16].

AIM OF THE WORK

In the current study, we aimed to assess the role of TH in the diagnosis of BM infiltration in NB patients.

PATIENTS AND METHODS

The present study is a prospective case control study. It was conducted at Pediatric Oncology Department, National Cancer Institute [NCI], Cairo University during the period from January 2014 to December 2016. The study included a homogenous convenience sample of 104 consecutive children with established diagnosis of NB. None of the recruited patients was excluded from the study. In addition, there was a control group that included 25 age and sex-matched healthy donors for bone marrow transplantation at NCI. Patients were subjected to full clinical examination and laboratory workup including serum neuron specific enolase [NSE], serum ferritin, and MYCN amplification by chromogenic in situ hybridization [CISH]. The radiological evaluation included bone scan and meta-iodobenzylguanidine [MIBG] assessment.

Pathological sampling

Potassium ethylene diamine tetra-acetic acid [K-EDTA] was used to collect BM aspirate specimens which were stained with May-Grunwald Giemsa stain. Staging of NB was accomplished by aid of BM trephine biopsy [BMB] stained by hematoxylin and eosin [H&E] and for immuno-histochemistry staining for NSE and Synaptophysin **[Figure 1A, 1B, 1C]**.

Assessment of TH expression by Quantitative Real-time [qRT-PCR]: QIAamp RNA extraction blood Mini kit [QIAGEN, cat no. 52304] was used to extract total RNA from bone marrow cells according to the manufacturer's instructions. Extracted RNA purity and

concentration was detected using spectrophotometer Nano-drop [Quawell, Q-500, Scribner, USA]. High Capacity cDNA Reverse Transcription Kit [Applied Biosystems, cat no. 4368814] was used for retro-transcription [cDNA]. Ready Made Assay, Taqman primer probe for TH mRNA [Thermo Fisher Scientific, USA, cat no: CA 94566] was used for TH mRNA expression quantification. The qRT-PCR was performed using a total volume of 20µl, and the thermal reaction conditions were as follows: polymerase activation: 95˚C for 10 min, followed by denaturation: 40 cycles of 95˚C for 30s, annealing and extension: 60˚C for 60s, in which fluorescence was acquired and detected by StepOne Real-Time PCR System [Applied Bio-systems, Foster City, CA, USA]. Data were expressed as relative quantification [RQ].

Statistical analysis: Data were analyzed using the statistical package SPSS [version 24 for Windows; SPSS Inc, Chicago, IL, USA]. Data were presented as number and percent or median and range. Variables were compared using chi-square test or Mann-Whitney U test as appropriate. A likelihood test was used to detect sensitivity and specificity of the variables. Kaplan Meier analysis was used to assess the survival rates of the patients. P-values less than 0.05 were considered statistically significant.

RESULTS

The current study included 104 NB patients with equal sex distribution and a median [range] age of 3.5 [0.2-16] years. Forty two patients presented with stage 3 [40.4%] and 62 [59.6%] with stage 4. Patients were classified according to the International Neuroblastoma Risk Group [INRG] staging system [17] into low: 0/104 [0%], intermediate: 38/104 [36.5%] and high risk patients: 66/104 [63.5%]. There were 44 [42.3%] patients positive for NMYC amplification and 40 [45.5%] patients positive for NSE expression. At the end of the study, there were 10 [9.6%] patients with relapsed disease, 8 [7.7%] patients died, and 96 [92.3%] were alive [Table 1].

Tyrosine hydroxylase expression levels in NB patients: TH was expressed in the BM samples of 78 [75%] patients and it was not expressed in the control group. The median expression of TH in NB patients was 29.7 with a range of [0- 277750]. Patients were classified according to the median expression of TH into patients with low expression [<29.7] and patients with over-expression [>29.7] [Figure 2].

Association between BM infiltration and the clinical and laboratory data; BM infiltration was detected in 58 patients [55.8 %]. It was shown that patients with BM infiltration had significantly higher levels of TH expression when compared to patients without [median [range]: 193 [0-277750] versus 4 [0-7849], p=0.003]. Also, BM infiltration was significantly associated with increased serum levels of ferritin and NSE, older age, advanced disease stage, high risk disease, positive BM staining for Synaptophysin and for H & E. Moreover, BM infiltration was significantly related to poor response to treatment and increased relapse and mortality rates [Table 2]. No significant association was found between TH expression and DFS and OS [Figure 3A, 3B]. However, it was found that patients with BM infiltration had significantly reduced DFS and OS durations [Figure 3C, 3D].

Performance of TH expression in detection of BM infiltration: The diagnostic power of TH for BM infiltration was assessed in relation to MIBG. The sensitivity, specificity, positive predictive value [PPV] and negative predictive value [NPV] for TH were [55.2%, 65.2%, 66.7% and 53.6%; respectively, [**P=0.048, Table 3**].

Association between TH expression and clinical and laboratory features: As compared to patients with low expression, patients with high expression had significantly higher serum ferritin levels [median [range]: 159 [7-3541] versus 95 [20-522] ng/mL, p=0.007], and significantly higher frequency of high-risk patients [75.0 % versus 53.6%, p=0.027]. Patients with high TH expression had significantly higher frequency of BM infiltration when compared to those with low TH expression [66.7 % versus 33.3 %, p=0.048]. On the other hand, there was no significant association detected between TH expression and the other clinical features including age, sex, synapto-physin expression, serum NSE, response to treatment, incidence of death and relapse **[Table 4].**

Table [1]: Clinical features of neuroblastoma patients

Patients' parameter		Frequency	Percent [%]
Age	Median [range]	3.5 [0.2-16]	
	Mean± SD	3.7 ± 2.78	
Gender	Male	52	50.0
	Female	52	50.0
serum NSE	Median [range]	212 [21.5-2066]	
serum Ferritin	Median [range]	131 [6.9- 3541]	
Stage	3	42	40.4
	4	62	59.6
Cytogenetic risk	Intermediate	38	36.5
	High	66	63.5
H&E	Negative	36	51.4
	Positive	34	48.6
Synaptophysin	Negative	48	54.5
	Positive	40	45.5
Tyrosine Hydroxylase	Negative	26	25.0
	Positive	78	75.0
MIBG	Negative	46	44.2
	Positive	58	55.8
Bone scan	Negative	46	44.2
	Positive	58	55.8
NMYC	Negative	60	57.7
	Positive	44	42.3
Response to treatment	Stationary	38	38.8
	Progressive	60	61.2
Relapse		10	9.6
Death	Live	96	92.3
	Dead	8	7.7

NSE: neuron specific enolase; MIBG: meta-iodobenzylguanidine

Table [2]: Assessment of bone marrow infiltration in NB patients

		Bone marrow infiltration		P value
		positive	negative	
Age		4 [0.7-8]	2 [0.2-16]	0.003
Sex	Male	26 [44.8%]	26 [56.5%]	0.324
	Female	32 [55.2%]	20 [43.5%]	
TH [RQ]		193 [0-277750]	4 [0- 7849]	0.003
Serum NSE		322 [24-2066]	114 [22-550]	P<0.001
Serum Ferritin		150 [20-3541]	75 [7- 2597	0.039
Stage	3	6 [10.3%]	36 [78.3%]	P<0.001
	4	52 [89.7%]	10 [21.7%]	
Risk	Intermediate	0 [0.0%]	38 [82.6%]	P<0.001
	High	58 [100%]	8 [17.4%]	
Synaptophysin	Positive	32 [59.3%]	8 [23.5%]	0.002
	Negative	22 [40.7%]	26 [76.5%]	
NMYC	Negative	36 [62.1%]	24 [52.2%]	0.326
	Positive	22 [37.9%]	22 [47.8%]	
H&E	Negative	10 [26.3%]	26 [81.3%]	P<0.001
	Positive	28 [73.7%]	6 [18.8%]	
Response to treatment	Responding	4 [6.9%]	34 [85%]	P<0.001
	Non-responding	54 [93.1%]	6 [15%]	
Relapse	No	50 [86.2%]	44 [95.6%]	0.021
	Yes	8 [13.8%]	2[4.4%]	
Death	Live	53 [91.4%]	43 [93.5%]	0.001
	Dead	5 [8.6%]	3 [6.5%]	

TH: Tyrosine hydroxylase, H & E: Hematoxylin and Eosin

Table [3]: Assessment of the diagnostic power of Synaptophysin and tyrosine hydroxylase [TH] for bone marrow infiltration

	Sensitivity	Specificity	PPV	NPV	P value
Synaptophysin	**59.3%**	**76.5%**	**80%**	**54.2%**	**0.002**
TH	**55.2%**	**65.2%**	**66.7%**	**53.6%**	**0.048**

NPV: Negative Predictive Value, PPV: Positive Predictive Value

Table [4]: Association between TH expression and the clinical features of the patients

		Tyrosine Hydroxylase expression		P value
		Low-expression	overexpression	
Age		3 [0.4-16]	4 [0.2-8]	0.752
Sex	**Male**	32 [57.1%]	20 [41.7%]	0.168
	Female	24 [42.9%]	28 [58.3%]	
Serum NSE [ng/mL]		291 [21- 2066]	189 [22-1426]	0.167
Serum Ferritin [ng/mL]		95 [20- 522]	159 [7-3541]	0.007
Stage	**3**	22 [39.3%]	20 [41.7%]	0.843
	4	34 [60.7%]	28 [58.3%]	
Risk	**Intermediate**	26 [46.4%]	12 [25.0%]	0.027
	High	30 [53.6%]	36 [75.0%]	
H&E	**Negative**	22 [52.4%]	14 [50.0%]	0.845
	Positive	20 [47.6%]	14 [50.0%]	
Synaptophysin	**Negative**	28 [58.3%]	20 [50.0%]	0.520
	Positive	20 [41.7%]	20 [50.0%]	
MIBG	**Negative**	30 [53.6%]	16 [33.3%]	0.048
	Positive	26 [46.4%]	32 [66.7%]	
NMYC	**Negative**	36 [64.3%]	24 [50.0%]	0.166
	Positive	20 [35.7%]	24 [50.0%]	
Death	**Live**	52 [92.9%]	44 [91.7%]	0.820
	Dead	4 [7.1%]	4 [8.3%]	
Relapse	**No**	52 [92.9%]	42 [87.5%]	0.507
	Yes	4 [7.1%]	6 [12.5%]	
Response to treatment	**Responding**	24 [46.2%]	14 [30.4%]	0.146
	not responding	28 [53.8%]	32 [69.6%]	

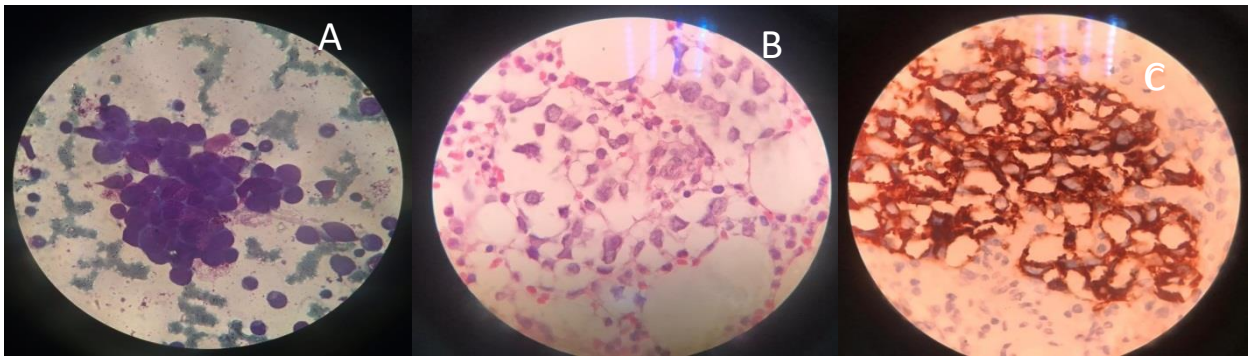

Figure 1: A] Bone marrow aspirate infiltration stained with May-Grunwald Giemsa **[*100], B]** Bone marrow biopsy infiltration stained by H&E **[*100], C]** Bone marrow biopsy infiltration stained with syaptophysin

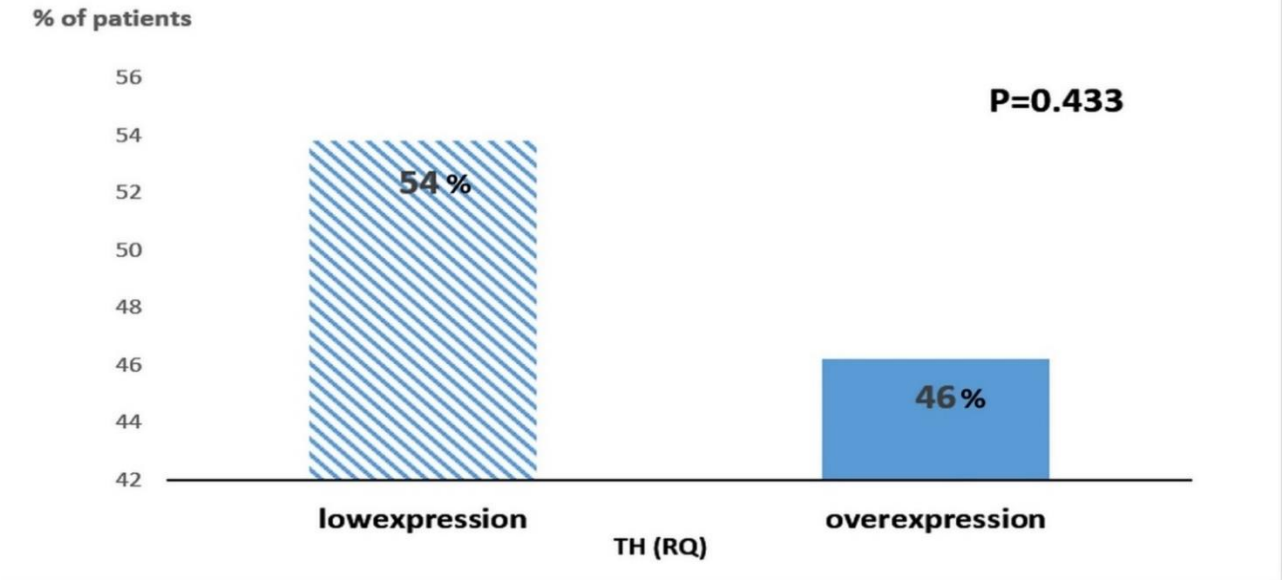

Figure [2]: Expression level of Tyrosine hydroxylase [TH] enzyme in the bone marrow aspirate of neuroblastoma patients

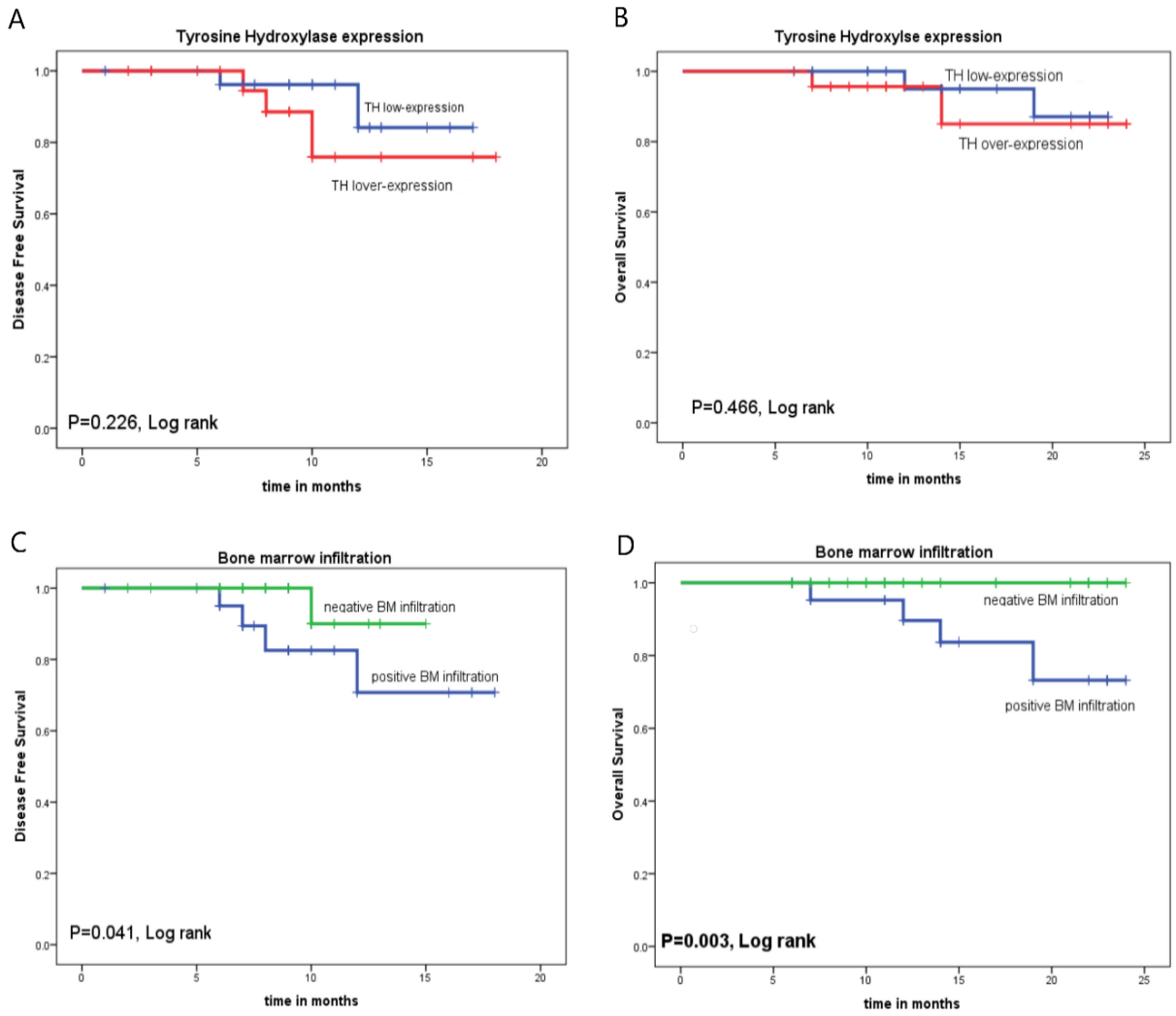

Figure [3]: Association between Tyrosine hydroxylase [TH] expression and: A] DFS, B] OS rates of the patients. Association between bone marrow infiltration and: C] DFS, D] OS rates of the patients.

DISCUSSION

Patients with NB have reduced survival rates and increased incidence of relapse even in those with intermediate or low risk [18, 19]. Considering the fact that BM infiltration is a predictor of poor outcome in those patients, better prediction of this pathology is of crucial importance.

Previous studies proposed that the assessment of BM infiltration and MRD evaluation at a molecular level had more prognostic significance than the assessment of the number of tumor cells infiltrating the BM [20, 21].

The present study aimed to assess the role of TH expression in detection of BM infiltration in NB patients. The study also showed a significant association between TH expression and bone marrow involvement. These data are in agreement with previously published studies that identified TH enzyme as a sensitive molecular biomarker for bone marrow involvement in NB patients [20, 22].

Viprey et al. [23] concluded that the molecular detection of TH is a reliable method for assessment of BM involvement, with good sensitivity. In addition, we found that BM infiltration was significantly associated with adverse events such as high risk classification, advanced disease stage, poor response to treatment, increased serum levels of ferritin and NSE, positive BM staining for Synaptophysin and H&E and reduced DFS and OS rates. These data are in consistence with Druy et al. [20], who concluded that the presence of BM disease at the primary diagnosis is considered a significant adverse prognostic factor with reduced DFS and OS rates of NB patients.

The current study showed that TH was expressed in the BM samples of 75% of the assessed patients, and it was negative in normal control subjects. TH was significantly overexpressed in high risk group patients, and in those who had increased serum levels of ferritin. These data are consistent with many previous studies reported that serum ferritin is a poor prognostic factor for NB patients, and significantly associated with decreased survival rates [18, 24,25].

Also, Träger et al. [26] found a significant expression of TH in the BM of patients with stage 4 compared to those with stage 1-3. In a recent study published by Lee et al. [27], they observed a significant increase of TH expression levels in high-risk patients than in low- or intermediate-risk patients, when it was assessed in the peripheral blood of the patients.

Conclusions:

TH may serve as a useful tool for diagnosis of BM infiltration in NB. BM infiltration is associated with poor DFS and OS.

Limitations:

Conclusions of the present study are limited by the fact that it is a single-center study.

Compliance with ethical standards

The study protocol was approved by the IRB of NCI, Cairo University, in line with 2011 declaration of Helsinki. A written informed consent was signed by the guardians of children prior to enrollment in the study.

Conflict of interest:

All authors declare that there was no possible conflict of interest.

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