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Role Of Neuron-Specific Enolase and Ferritin in Neuroblastoma and Wilms Tumor

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ABSTRACT

The role of enolase isozymes and ferritin as biomarkers in pediatric solid tumors, including neuroblastoma and Wilms tumor. While neuron-specific enolase (NSE) is well-established in neuroendocrine tumors, its expression patterns and prognostic significance in other childhood cancers remain underexplored. Similarly, ferritin, traditionally linked to iron metabolism and inflammation, may have unrecognized associations with tumor aggressiveness or treatment response in these malignancies. dysregulated enolase isoforms and altered ferritin levels correlate with disease progression, metastatic potential, or therapeutic outcomes in pediatric solid tumors. Patient and methods: This case-control study, conducted at Baghdad Teaching Hospital (February–December 2024), evaluated Neuron-Specific Enolase (NSE) and ferritin as potential biomarkers in pediatric solid tumors. The study included 98 children under 10 years old, divided into three groups: 34 neuroblastoma patients, 31 Wilms tumor patients, and 33 healthy controls. Serum levels of NSE and ferritin were measured using Sandwich ELISA. This case-control study evaluated serum neuron-specific enolase (NSE) and ferritin levels in pediatric solid tumors. Neuroblastoma patients exhibited dramatically elevated NSE (424.71±326.17 ng/mL; 43-fold higher than controls, $p<0.001$) and significantly higher levels than Wilms tumor cases (175.45±97.41 ng/mL, $p<0.001$). Conversely, Wilms tumor patients showed the highest ferritin levels (505.84±266.58 µg/L; 7.9-fold above controls, $p<0.001$), significantly exceeding neuroblastoma values (324.12±138.11 µg/L, $p<0.001$). These findings demonstrate distinct biomarker profiles: NSE shows exceptional elevation in neuroblastoma, while ferritin is markedly increased in Wilms tumor, suggesting their potential diagnostic utility in differentiating these pediatric malignancies.

Keyword: *neuron-specific enolase, ferritin, neuroblastoma, wilms tumor*

1. INTRODUCTION

Neuroblastoma, arising from neural crest elements of the sympathetic nervous system, is the most common extracranial solid tumor of childhood. Wilms tumor or nephroblastoma affects the kidneys and is the most prevalent renal tumor in this age group. Hepatoblastoma, although rare, is the most common liver tumor in young children, typically presenting before the age of three(1).

Wilms tumor, also called nephroblastoma, is the most common type of renal tumor in children. It gets its name from Max Wilms, a German surgeon who first documented 8 cases of "mixed tumors" made of both blastema and tubules in 1899 (2). Approximately 75% of Wilms tumors are diagnosed before the age of 5, with the median age of diagnosis at 3 years old. Wilms tumor accounts for 6% of all childhood cancers and occurs most frequently in black patients (3). While the majority of cases are unilateral, children may have bilateral disease in 5% to 10% of cases. Despite being aggressive, Wilms tumors have a relatively high cure rate. Survival rates can range from 80-90% for patients classified as "low risk" while being around 75% for "intermediate-risk" patients. "High-risk" patients have survival rates below 50% (4).

In humans, three different enolase isozymes exist: α-, β-, and γ-enolase, coded by the genes Eno1 on chromosome 1q23.2, eno3 on chromosome 17q21-q22, and eno2 on chromosome 12p13, coding the α, β, and γ subunits, respectively(5). Among these, NSE represents the most tissue-specific isoenzyme, as it is highly expressed in neurons and cells of neuroendocrine origin, comprising more than 90% of total soluble proteins in neuroepithelial cells. Enolases are coded by different genes and must be synthesized separately prior to forming the dimeric isoform(6). Each subunit has about 436 amino acid residues and a molecular mass of approximately 47 kDa. The three isozymes have a similar secondary and tertiary structure, composed of both α-helices and β-sheets, as well as mainly β-strands, which are located in the inside of the molecule, forming a

hydrophobic core. The active enzyme is a dimer of three isoforms of approximately 80 kDa(7).

Ferritin is a protein complex that stores iron in a soluble and non-toxic form, thereby ensuring that the body has a reserve of iron that can be easily mobilized when necessary. It is present in a wide range of cell types, with a particular emphasis on liver cells, spleen, and bone marrow. The protein shell of ferritin is essential for iron homeostasis, as it encases up to 4500 iron ions in its central cavity.(8).

Ferritin serves primarily as an iron storage molecule; it plays a crucial role in regulating the body's iron levels. By sequestering iron, ferritin reduces the amount of free iron in the body, which can catalyze the formation of harmful free radicals. Through its ferroxidase activity, ferritin also helps convert iron from its ferrous (Fe2+) to ferric (Fe3+) form, the state in which iron can be safely stored within the ferritin molecule (9).

Ferritin levels in the blood can serve as a biomarker for various conditions. Low ferritin levels typically indicate iron deficiency, which can lead to anemia. Conversely, high levels of ferritin can indicate conditions such as hemochromatosis, inflammation, liver disease, or malignancy. It is often used in conjunction with other tests to diagnose and monitor these conditions(10).

2. PATIENTS AND METHODS

This case-control study was conducted in Baghdad Teaching Hospital/Medical City/Baghdad/Iraq by the Department of Biochemistry/College of Medicine/University of Baghdad **between February 2024 and December 2024**. It included 98 subjects below 10 years with clinical diagnosis of solid tumors, including neuroblastoma and Wilms tumors, compared with controls. Subjects were divided into Group I, which included 34 subjects with neuroblastoma; Group II, which included 31 subjects with Wilms tumors; and Group III, which included 33 healthy children.

The scientific and ethical committees of the Department of Biochemistry, College of Medicine, University of Baghdad approved this study. Ethical approval was obtained from Baghdad Teaching Hospital / Medical City Complex and the Ministry of Health / Iraq. Verbal consent was obtained from the subjects in this study. Exclusion criteria included patients with other types of solid tumors and children with Wilms' tumor and neuroblastoma above 10 years.

Five milliliters (5ml) of blood were aspirated from the peripheral vein of each subject of the three groups and allowed to clot for 15 minutes, then centrifuged for 10 minutes at 2500 rpm. The separated serum was stored at - 45ºC till the day of lab testing, which included measurement of Neuron Specific Enolase and ferritin by Sandwich ELISA.

SPSS software, version 25.0, was used to conduct statistical analyses (SPSS, Chicago). The mean and standard deviation of the data with a normal distribution were displayed, and the analysis of variance (ANOVA) test was performed.

3. RESULTS

The study compared serum neuron-specific enolase (NSE) levels across neuroblastoma, Wilms tumor, and healthy control groups. As shown in figure 1, Neuroblastoma patients showed dramatically elevated NSE levels (mean 424.71 ± 326.17 ng/mL), approximately 43-fold higher than controls (9.79 ± 5.04 ng/mL) and over twice the levels seen in Wilms tumor (175.45 ± 97.41 ng/mL, 18-fold higher than controls). Statistical analysis (one-way ANOVA, $p<0.001$) confirmed significant differences across all groups, with pairwise comparisons also highly significant (neuroblastoma vs. Wilms tumor: $p<0.001$; neuroblastoma vs. control: $p<0.001$; Wilms tumor vs. control: $p=0.004$).

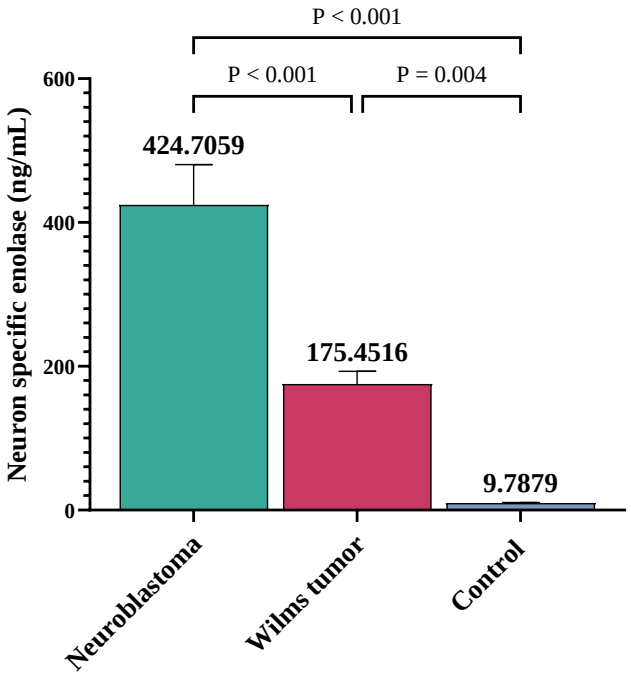

Figure 1 Comparison of mean serum neuron-specific enolase levels (ng/mL) among neuroblastoma, Wilms tumor, and control groups. Error bars represent standard deviation.

Ferritin levels across Wilms tumor, neuroblastoma, and healthy control groups. As shown in Figure 2, Wilms tumor patients exhibited the highest ferritin levels (mean 505.84 ± 266.58 µg/L), 7.9-fold higher than controls (64.42 ± 8.63 µg/L) and significantly elevated compared to neuroblastoma (324.12 ± 138.11 µg/L, 5-fold higher than controls). Statistical analysis (one-way ANOVA, $p<0.001$) confirmed significant differences, with all pairwise comparisons (Wilms vs. neuroblastoma: $p<0.001$; Wilms vs. control: $p<0.001$; neuroblastoma vs. control: $p<0.001$) showing robust significance.

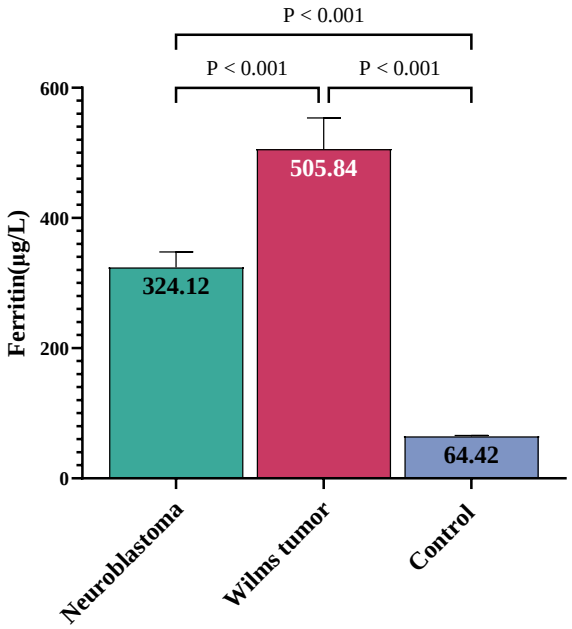

Figure 2 Comparison of mean serum ferritin levels (µg/L) among neuroblastoma, Wilms tumor, and control groups. Error bars represent standard error of means. All pairwise comparisons demonstrated highly statistically significant differences (p<0.001).

4. DISCUSSION

Neuroblastoma cells can synthesize Ferritin, with synthesis regulated by exogenous iron. In studies, the incorporation of radiolabeled leucine into Ferritin was observed, confirming the tumor's ability to produce this protein (11).Elevated serum ferritin levels are often linked to the tumor's activity, particularly in advanced stages (III and IV) (12).Neuroblastoma tumors produce basic and acidic isoferritins, with serum levels showing a significant correlation between these variants. Increased basic ferritins always accompany high levels of acidic ferritins. The ratio of acidic to basic ferritins remains consistent across samples, suggesting a stable production mechanism within the tumor (13).Elevated serum ferritin serves as a tumor marker, but its interpretation must consider factors like blood transfusions, which can also raise ferritin levels (12).The presence of Ferritin in neuroblastoma may be linked to tumorigenesis, indicating a potential role in disease progression (14).Conversely, while elevated Ferritin is a valuable marker for neuroblastoma, it is essential to interpret these levels cautiously, as they can be influenced by other factors, such as iron load from transfusions, which may complicate the assessment of tumor activity(12).

Ferritin has emerged as a significant biomarker and therapeutic target in the context of Wilms tumor, a common pediatric kidney cancer. Recent studies indicate that Ferritin serves as an iron storage protein and plays a role in tumorigenesis and cancer progression. Elevated serum ferritin levels have been associated with various malignancies, including breast cancer, indicating its potential as a prognostic marker (15).In Wilms tumor, similar mechanisms may apply, where increased ferritin levels could correlate with tumor presence or progression. Ferritin is secreted by tumor-associated macrophages, contributing to tumor growth and inflammation. It has been shown to stimulate the proliferation of cancer cells in an iron-independent manner, suggesting a direct role in tumorigenesis(16) .Ferritin's ability to target tumor cells via transferrin receptor 1 makes it a promising vehicle for drug delivery in cancer therapy(17).Ferritin nanoparticles can be engineered to enhance imaging and treatment, providing a dual function in cancer management(18)

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