Neuron Specific Enolase, a Biomarker of Breast Cancer Cerebral Metastasis

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Abstract

Introduction: The diagnosis of brain metastasis and/or epilepsy remains a challenge in neurological symptomatic and asymptomatic cancer patients. Despite improved imagery and clinical approach, an early diagnosis requires more tools. Neuron Specific Enolase (NSE) is a specific molecular marker for mature nerve cells dosed at high levels in fetal and early postnatal brain, and is also a tumor marker in some types of neuroendocrine tumors. This is a two group, non-randomized study on sixty patients with breast cancer diagnosis. The main objective was to document the potential contribution of the NSE marker to the diagnosis of cerebral parenchyma metastasis. The second objective was to determine the predictive value of this marker in relation with the brain metastasis evolution. Patients and Methods: Patients with brain metastasis (BM) were matched with patients with no brain metastasis (NBM), using age and breast cancer subtype (luminal A, luminal B, triple negative, HER2 positive), as matching factors. The NSE level was measured one time for all the patients in the study—exceptions are detailed in the text. Results: Sixty breast cancer patients were included in the study, 30 in each group. Twenty-one BM patients were matched with twenty-one NBM patients. We observed a significantly increased level of the NSE in the BM group with a median value of 48.4 ng/ml (min 21.0 to max 349.2) compared to a median of 18.4 ng/ml (4.5 to 28.0) in NBM, P-value <0.001. Evidently increased values of the NSE were also observed in the non matched patients. NSE standard value was inferior to 18 ng/mL according to our institution laboratory (Porte de Hal Medical Analysis Laboratory, Brussels, Belgium). Conclusions: Data resulting from the above study supports the contribution of NSE to the diagnosis of breast cancer brain metastases, before MRI or sometimes CSF examination. As shown this marker could become a tool of diagnosis of brain metastasis.

Subject Areas

Neurology, Oncology

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Keywords
Neuron Specific Enolase (NSE), Breast Cancer, Brain Metastasis

1. Introduction

The enolase is a glycolytic isoenzyme that catalyses the conversion of 2-phosphoglycerate to phosphoenolpyruvate. Three homo and heterodimeric forms of this enzyme are distinguished: alpha, beta, and gamma.

The dominant enolase-isoenzyme is the gamma form or neuron-specific enolase (NSE), a 75 kD homodimer. It is found primarily in the peripheral neurons and neuro-endocrine tissues, but also in platelets, megakaryocytes, erythrocytes, T-cells, striated and smooth muscle cells. NSE has also been found in neuroendocrine tumors, glioblastomas, meningiomas and pheochromocytoma [1] [2] [3]. Some neurological disorders like Alzheimer disease, Huntington disease and amyotrophic latero-sclerosis (ALS) are accompanied by an increased value of the NSE level in the spinal fluid and serum.

The normal value is inferior to 18 ng/mL (Porte de Hal Medical Analysis Laboratory, Brussels, Belgium). The biological half-life in the body fluids is approximately 24 hours. The neuronal destruction can cause a release of NSE with high concentrations lasting for 36, even 48 hours [4] [5] [6] [7] [8]. Therefore the measurement of NSE has been used to differentiate the diagnosis of the neuron-destructive and neuron degenerative disorders such as brain injury, encephalitis, stroke, recent epileptic seizures and dementia [9]-[17].

Royds et al. [18] published in 1983 the first data on the role of NSE in the neurological diseases, showing that the gamma neuron enolase in a sensitive marker of neuronal tissue damage.

In extension to the indicative value of the NSE level after neuronal lesions, the hypoxic lesions could be more easily predicted and evaluated after stroke episodes using the dosage of the gamma enolase. After cardiac arrest the outcome is mostly determined by the degree of hypoxic damage, patients recovered after cardio-pulmonary resuscitation being at great risk of vegetative state and even coma. Several chemicals are released from the brain into the blood and cerebrospinal fluid after cardiac arrest and the serum concentration of neuron-specific enolase (NSE) has appeared promising as a predictor of a poor outcome.

In a cohort study on forty-five resuscitated patients [18] blood samples for NSE measurement were collected between 12 and 36 hours after the cardiac arrest. The outcome was evaluated 6 months later with the Glasgow Outcome Scale (GOS). Based on the Glasgow scale patients were divided in two groups, the first group of 34 patients with GOS 1 and 2, and the second group of 11 patients with a GOS at 3, 4 and 5. Results showed significantly higher level in the first group—median 44.24 ng/dL, than those in the second group—median 25.26 ng/dL. In the first group, 30 patients died and four remained in a vegetative state. In group 2, nine patients had favorable outcome: eight survived with mi-
nimal disability and one with severe disability.

These results should draw the physician attention on the importance of the NSE level in the prognostic of the patients with a difficult clinical and imagistic evaluation. One should question if the NSE should become a standard in evaluating the outcome of these patients, as it is the enzyme secreted by the damaged neurons [19].

Keeping in mind these results, the metastatic dissemination in the cerebral parenchyma is considered a cause of neuronal damage resulting in increased levels of the NSE marker.

A study published in 1995 by De Giorgio et al. [7], on a group on 19 patients, brought to light increased values of the NSE in the status epilepticus pathology with a peak within 24 to 48 hours after the epileptic episode. Following the same idea another study on the neuronal injury marker, NSE, was conducted in children with continuous and discontinuous epileptic activity, significant differences being established between the two groups [20].

Physicians showed the utility of this biomarker in the differential diagnosis of the neuronal or non-neuronal damaging pathology [1] [9] [21] [22]. In a study on 185 patients, Lee SY and all [9] showed the role on NSE in the differential diagnosis of seizure and syncope, based on an evident difference between seizure group 14 ± 7.57 ng/dL, syncope group 10.15 ± 3.22 and the control group 10.03 ± 1.28 ng/dL. These results may be explained by the absence of the neuronal injury in the syncope pathology and therefore the normal value of the neuron enolase.

NSE is also a tumor marker, especially in lung and neuroendocrine cancers, but according to our knowledge it has never been used as a marker of central nervous system metastatic lesions.

2. Patients and Methods

This study has been concluded at the Jules Bordet Institute-Brussels, between 2010-2014, on two groups of 30 patients each with an anatomopathological confirmed breast cancer diagnosis and ages between 34 and 71 years old.

The study has been approved by the Jules Bordet Ethic Committee and all patient signed an Informed consent.

The first group also called the “control group” included patients with a breast cancer diagnosis but no brain metastasis—NBM group.

The second group included breast cancer patients with cerebral metastasis – BM group.

In both groups a cerebral MRI, no older than two weeks before inclusion, confirmed the presence or absence of brain metastasis.

Patients in both groups had a serum evaluation of the NSE value at the inclusion in the study. Two exceptions are detailed below in the text.

Patients with brain metastasis (BM) were matched with patients with no brain metastasis (NBM), using age and breast cancer molecular subtype (luminal A, luminal B, triple negative, HER2 positive) as matching factors. Twenty-one pairs cases-control were obtained (see Table 1).
Table 1. All 42 patients characterized by age, metastatic site, subtype of BC and NSE value. BM : brain metastases group; NBM : no brain metastasis group; HER 2+ = HER 2 positive; TN: triple negative.

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<th>Subtype of BC</th>
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<td>HER2 +</td>
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<td>TN</td>
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2.1. Inclusion Criteria

All patients were required to have an age superior to 18 years, a breast cancer confirmed diagnosis and a cerebral magnetic resonance examination to confirm the presence or the absence of the brain metastasis. The magnetic resonance was no older than two weeks before inclusion.
2.2. Exclusion Criteria

Any patient with a neuro-endocrine tumor history was excluded from the study and also all the patients with a history or a recent diagnostic of brain tumors, epileptic seizures, stroke, dementia, or any brain injury other than the metastatic one.

A radiotherapeutic or intrathecal treatment less than one month before participation in this study was considered as exclusion criteria also.

2.3. Statistical Methods

NSE values between patients with and without cerebral metastases were compared using the Mann-Whitney test. The diagnostic performance of NSE regarding cerebral metastases was expressed in terms of the area under the ROC curve, sensitivity and specificity (with 95% confidence intervals). All statistical analyses were performed using the SAS System version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results and Discussion

Sixty patients were included in the study, thirty for each group. Twenty-one patients from the No Brain Metastasis group were matched with twenty-one patients from the Brain Metastasis group. Matching was based on breast cancer molecular subtype and age, as follows: 2 patients (5%) with HER2 positive, 16 patients (38%) with luminal A, 22 patients (52%) with luminal B and 2 patients (5%) with triple negative disease (see Table 1).

Matching patients by metastatic site was not feasible, as most of the patients with brain secondary lesions had also a widely aggressive and long lasting treated systemic disease, meanwhile patients with no brain lesions had a lower burden systemic disease.

For the patients with HER2 positive and triple negative breast cancer, we could observe in the BM group a multi-site systemic metastatic disease, meanwhile for the NBM group no systemic lesion was detected at the inclusion in this study.

The luminal A and B groups had a heterogeneity of metastatic sites in the brain parenchyma and also in the systemic locations.

Anyway, independent of the molecular type, age or systemic disease dissemination patients with cerebral metastases had higher NSE values: median 48.4 ng/ml (min 21.0 to max 349.2) compared to a median of 18.4 ng/ml (4.5 to 28.0) in patients without cerebral metastases, P-value < 0.001 (see Figures 1-5).

We observed no correlation between the NSE value and number or volume of brain metastasis.

Also the Neurone Specific Enolase had an excellent diagnostic performance for predicting cerebral metastases: area under the ROC curve of 0.97 (95% CI, 0.92 to 1). With the cutoff of NSE ≥ 22 to predict cerebral metastases, we obtain a sensitivity of 20/21 = 95% (95% CI, 77% to 99%) and a specificity of 18/21 = 86% (95% CI, 65% to 95%) (see Figure 6).
Figure 1. All patients included in the study were matched based on the subtype of breast cancer. Light red bar: luminal A with BM, Green bar: luminal A with NBM; Rose bar: luminal B with BM, Mauve bar: luminal B with NBM; Orange bar: HER2 positive with BM, Light green bar: HER2 positive with NBM; Dark red bar: Triple negative with BM, Dark blue: Triple negative with NBM.

Figure 2. Patients with luminal A breast cancer.

Figure 3. Patients with luminal B breast cancer.
Results obtained from this study sustain our hypothesis of clinical use of the Neurone Specific Enolase biologic marker in the diagnosis of brain metastases. In the era of advanced medicine Magnetic Resonance Imagery is the standard exam in the detection and follow up of brain metastasis, although limited by the costs and interval between two examinations.
Based on the supporting results of this study, NSE could be used more easily and more frequently in clinic for the detection of brain metastasis.

We discuss the case of two patients in more detail.

The first is the case of a young female patient with luminal B breast cancer and cerebral parenchymal metastasis already treated with radiotherapy, last treatment one year before inclusion in the study.

After consent of the patient to have more than two controls of the NSE, we followed the value of this marker during the brain metastasis evolution. This patient had a first dosage of the NSE marker at the inclusion in our study at the same time with a cerebral MRI showing the progression of brain lesions.

In Figure 7 one can observe the sensible correlation of the NSE value and the evolution of the parenchymal dissemination. We note that in the period from April 2013 and August 2013 the patient had multiple cerebral MRI examinations each time indicating a stable disease according to RECIST1.1 criteria [23]. If we closely examine the MRI images we can actually observe a slight progression of the lesions (see Figure 7). We could hypothesize that the NSE is a much more sensible marker correlated to the brain lesions evolution even before a clear progression on the MRI.

The second case is one 70 years old patient included initially in the No Brain Metastasis group (following the MRI results) with a NSE level that had been measured at 21.2 ng/mL.

The anatomopathology of this patient’s breast cancer showed an invasive ductal carcinoma, oestrogen and progesterone receptors positive, HER2 negative. The diagnosis was done in 1991, and in august 2011, at the moment of the first NSE dosage the patient presented cutaneous, pleural and bone metastases.

![Figure 7. The sensible corelation of the NSE value and the brain metastasis evolution on the cerebral MRI of one patient. We can observe an increasing value of the NSE correlated to a slight progression on the MRI caracterised as stable because of the RECIST1.1 criteria < 20%. ↑ = increased volume/number of cerebral metastases; SQ = statu quo in volume/number of the cerebral metastasis; ↓ = decreased of cerebral metastases.](image)
Five months later due to neurological degradation (dizziness and steppage) a cerebral magnetic resonance was done, and the images were compatible with parenchymal and leptomeningeal metastatic processes. At the second measurement, the neurone specific enzyme was almost doubled to 53.9 ng/dL. No radiotherapy treatment, or any history of dementia, epileptic seizure, stroke or cardiac arrest was documented for this patient in the period between the two measures of the NSE.

The case of the first patient cautions on the precision of this biologic marker in the detection and monitoring of the brain metastasis and thus in an earlier therapeutic attitude or more detailed surveillance.

The second case described encourages one to question on the predictive value of the NSE marker before clinical symptoms or imagery arguments. We sustain the fact that these patients should be considered “at risk” and a more systematic control of the NSE level and cerebral magnetic resonance examination should be programmed.

Anyway a larger group of patient is necessary to confirm these two hypothesis.

4. Conclusions

Data resulting from the above study proves the interest of using the Neurone Specific Enolase marker in the early diagnosis of central nervous system metastasis in the breast cancer patients, before or complementary to the cerebral MRI or, sometimes, CSF analysis.

Following this idea, the second future objective will be to determine the predictive value of the NSE in the brain metastasis evolution on a larger cohort longitudinal study.

Also the use of the Neurone Specific Enolase marker in the early detection of brain metastasis in patients with a higher risk of brain metastasis—HER2 positive and triple negative—would also be necessary.

Conflicts of Interest

The authors indicated no potential conflicts of interest.

Authors declare to have full control of all primary data and allow the journal to review the data if requested.

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