Plasma S100ß is not a useful biomarker for tumor burden in neurofibromatosis

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Plasma S100β is not a useful biomarker for tumor burden in neurofibromatosis

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Abstract

Objectives: Neurofibromatosis 1 (NF1), NF2, and schwannomatosis are characterized by a predisposition to develop multiple neurofibromas and schwannomas. Currently, there is no blood test to estimate tumor burden in patients with these disorders. We explored whether S100β would act as a biomarker of tumor burden in NF since S100β is a classic immunohistochemical marker of astrocytes, oligodendrocytes and Schwann cells and a small study showed S100β concentrations correlate with the volume of vestibular schwannomas.

Design and Methods: We calculated whole-body tumor burden in subjects with NF1, NF2, and schwannomatosis using whole-body MRI (WBMRI) and measured the concentration of S100β in plasma using ELISA. We used chi-square tests and Spearman rank correlations to test the relationship between S100β levels and whole-body tumor burden.

Results: 127 consecutive patients were enrolled in the study (69 NF1 patients, 28 NF2 patients, and 30 schwannomatosis patients). The median age was 40 years, 43% were male, median whole-body tumor volume was 26.9 ml. There was no relationship between the presence of internal tumors and the presence of detectable S100β in blood for the overall group or for individual diagnoses ($p > 0.05$ by chi-square for all comparisons). Similarly, there was no correlation between whole-body tumor volume and S100β concentration for the overall group or for individual diagnoses ($p > 0.05$ by Spearman for all comparisons).

Conclusions: Plasma S100β is not a useful biomarker for tumor burden in the neurofibromatoses. Further work is needed to identify a reliable biomarker of tumor burden in NF patients.

Keywords: S100B, neurofibroma, schwannoma, biomarker, neurofibromatosis

1. Introduction

The neurofibromatoses are a group of disorders characterized by a genetic predisposition to multiple nerve sheath tumors. The hallmark tumors in neurofibromatosis include neurofibromas in neurofibromatosis 1 (NF1) patients and schwannomas in NF2 and schwannomatosis patients. Currently, there is no non-invasive way to estimate tumor burden in these diseases. Biomarkers currently exist for other tumors, including prostate cancer (prostate specific antigen, PSA), ovarian cancer (CA-125), and germ cell tumors (alphafetoprotein, AFP). A biomarker for nerve sheath tumors could help clinical management of these diseases by screening symptomatic patients for an estimation of internal tumor burden.

The S100 family of calcium-binding proteins is predominantly expressed by astrocytes and Schwann cells and S100β is a classic immunohistochemical marker for these cells. S100β-secreting cells give rise to classic features of the neurofibromatoses including neurofibromas and schwannomas (Schwann cells) and gliomas (glial cells). The S100β subunit has been studied as a biomarker for many disorders, including stroke, traumatic brain injury and metastatic brain disease [1;2]. S100α1β and S100$\beta\beta$ are present in malignant tissues, such as melanoma, and have also been found in glioma, thyroid cell carcinoma, and renal cell carcinoma. Determination of S100β in serum has been shown to be clinically useful for prognosis and treatment monitoring of patients diagnosed with stage 3 malignant melanoma [3]. Furthermore, in one study, concentrations of S100β correlated with the volume of vestibular schwannomas [4], which are the hallmark tumor of neurofibromatosis 2. To date, the usefulness of S100β

levels in estimating internal neurofibroma and schwannoma tumor burden in NF has not been tested.

2. Material and methods

2.1 Patients and imaging

Samples used in this study were collected from a subset of patients enrolled in a prospective multicenter study of whole-body MRI scanning of subjects with NF1, NF2, and schwannomatosis. Whole-body MRI scans were collected as described previously [5]. In brief, subjects were imaged from head to ankles in the supine position using a 1.5 Tesla magnet, integrated body coil, and no intravenous contrast. Five acquisitions were used to image the entire body with a fat suppressed fluid sensitive STIR sequence. The five images were subsequently fused into a single whole body DICOM image. Non-central nervous system tumors were identified by a board-certified radiologist and total tumor volume was calculated using semi-automated analysis.

2.2 Enzyme linked immunosorbent assays

Blood samples were collected in EDTA-tubes and spun down at 5000x for 10 minutes at 4°C. Plasma was collected and immediately frozen at -80°C. A sandwich model enzyme linked immunosorbent assay (ELISA) (Alpco Diagnostics Ltd, Salem, NH, Catalog number, 48-S1BHU-E01) was used to measure levels of S100β in blood plasma samples. The measurable range of the assay was 98-6300 pg/ml and the normal physiological serum concentration is <200 pg/ml in adults [6].

2.3 Statistics

Descriptive statistics were calculated for whole-body tumor volume and S100β concentration for each disease group. Presence or absence of internal tumors and detectable S100β levels were compared using Chi-square test for categorical variables. The relationship between whole body tumor burden and S100β was analyzed using Spearman coefficients. Statistical analysis was performed using SAS Software (SAS Institute Inc., Cary, NC) and p-values less than 0.05 were considered statistically significant. The study was approved by the institutional review board at Massachusetts General Hospital (Partners Human Research Committee), which waived the requirement for informed consent for this secondary use of samples.

3. Results

We analyzed blood samples from 127 consecutive patients enrolled in the research study at Massachusetts General Hospital. This included 69 patients with NF1, 28 patients with NF2, and 30 patients with schwannomatosis. The whole body tumor volume and concentrations of S100β for each group is shown in Table 1. There was no relationship between the presence of internal neurofibromas or schwannomas and the presence of detectable S100β in plasma for the overall group or for individual diagnoses by chi-square (p > 0.05 for all comparisons). Similarly, there was no correlation between whole body tumor burden and S100β concentration for the overall group or for individual diagnoses (Fig. 1) (p > 0.05 for all comparisons).

4. Discussion

NF1, NF2, and schwannomatosis are characterized by phenotypic variability in the number and size of internal nerve sheath tumors both within families and between

families [7;8] MRI is the gold standard for identifying internal tumors but imaging the entire body is not practical or cost-efficient in the majority of clinical centers. An inexpensive and low-cost laboratory test would be helpful to screen patients for internal nerve sheath tumors. Previous studies suggest that concentrations of S100β may correlate with the size of vestibular schwannoma, which is the hallmark tumor of NF2 [4]. For this reason, we decided to study whether this marker would correlate with overall tumor burden in patients with a genetic predisposition to nerve sheath tumors (i.e., NF1, NF2, and schwannomatosis).

Our analysis revealed a wide range of S100β concentrations among patients. No detectable amounts of S100β were found in 75% of NF2 patients, 52% of NF1 patients, and 37% of schwannomatosis patients. Furthermore, there was no statistically significant correlation between S100β concentration and whole-body tumor burden. Based on this data, we hypothesize that neurofibromas and schwannomas do not release S100β directly into the circulation and that there is an alternative reason for the elevated concentrations seen previously with vestibular schwannomas [4].

The limitations of this study include modest patient numbers within each diagnosis group. Limited ability of WBMRI to image the internal auditory canal prevented us from confirming any relationship between vestibular schwannoma size and S100β levels in NF2 patients.   In addition, the WBMRI imaging protocol used does not account for the volume of cutaneous nerve sheath tumors in NF1 and NF2 patients, which may alter S100β expression.

To date, no reliable circulating biomarkers have been validated for nerve sheath tumors although adrenomedullin, MIA, and SOX9 have been suggested for future

development [9-11]. Proteomic analysis of plasma samples from NF and non-NF patients may help identify candidate proteins that correlate with tumor burden.


5. Conclusion

Our study does not support the use of plasma S100β as a biomarker for tumor burden in neurofibromatosis. Further work is needed to identify a reliable biomarker to screen NF patients for internal tumors without MRI scan.

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Figure 1. Relationship between whole-body tumor characteristics and S100β concentration in plasma for 127 patients with NF1, NF2, and schwannomatosis.
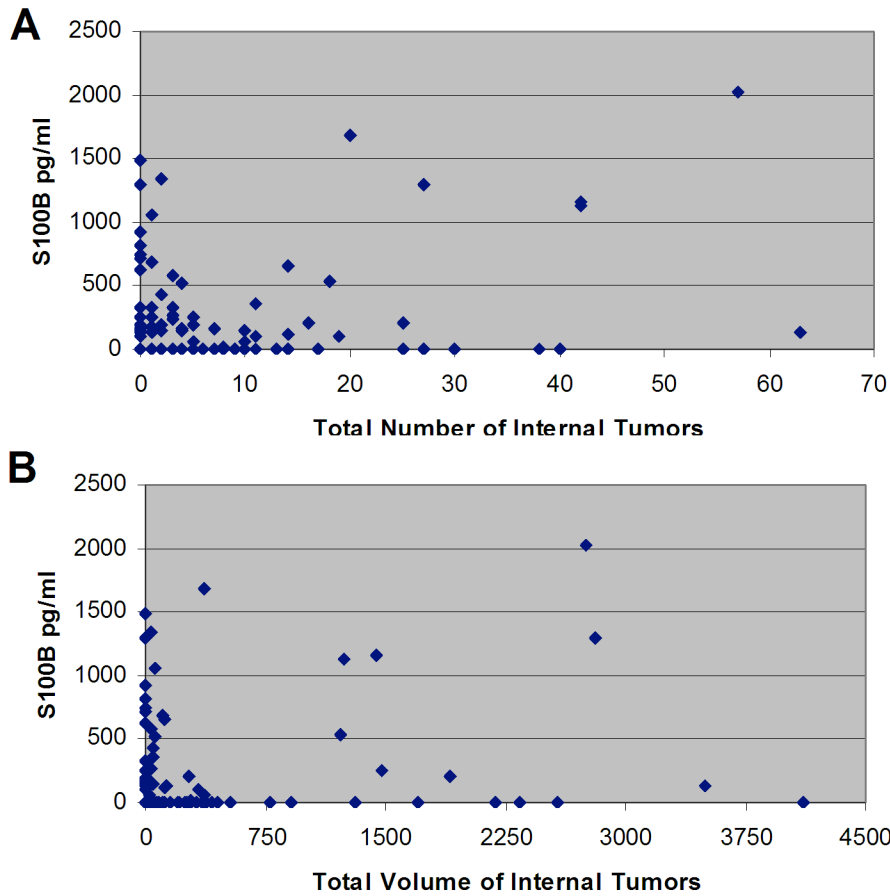
Panel A: Relationship between whole-body tumor number and S100β concentration.

Panel B: Relationship between whole-body tumor number and S100β concentration, displayed without an extreme outlier of subject with 9,106 ml of tumor and S100β level of 165 pg/ml.