

S-100 protein and melanoma

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Objective. S-100 is a Ca-binding protein which regulates phosphorylation depending on proteinkinase C. The main role of S-100 is to influence the so-called immune answer by Ca signal transduction. S-100 B is connected with melanoma. The aim of our work was to estimate the S-100 level in skin and eye melanoma patients and its agreement with literature data.

Materials and methods. We examined 21 patients with eye melanoma and 57 patients with skin melanoma, using ELISA S-100 Sangtec (Sweden) reagents, till 2004 inclusive, by the hemiluminiscence method (Elecsys, Roche).

Results. S-100 positivity in eye melanoma was 32% and in cutaneous melanoma 52%. High S-100 levels are associated with more advanced process, and patients with S-100 levels above the cut-off level need more frequent examination. Individual elevating of S-100 protein level is connected also with more unfavorable prognosis. **Conclusion.** S-100 could be used as a marker in eye melanoma.

Key words: S-100 protein, skin, eye melanoma

INTRODUCTION

The name of protein S-100 comes from its solubility in 100% ammonium sulfate at neutral pH. S-100 belongs to the EF protein family (17 proteins) (1, 2). It is a Ca-binding protein with the molecular weight of 21 kD. The gene coding S-100 protein is in 1q21 chromosome (3) and localized in the cell cytoplasm, mitochondria and nucleus, mostly in epithelial cells, neurons, astrocytes, glial cells, Schwann cells, satellite cells, sympathetic ganglions, melanocytes (4). S-100 protein is formed by 2 α and β subunits. α and β are found in melanocytes, glial cells, $\beta\beta$ in glial Schwann cells, $\alpha\alpha$ in striated muscle (ren, cor) (14). S-100 is a protein which regulates phosphorylation depending on proteinkinase C; it regulates also target fermental activity (glyceraldehyde-3-phosphatedehydrogenase, fructose 1,6-biphosphate aldolase). Therefore S-100 influences the microtubuli and in connection with annexin II influences cell endoexocytosis (5, 6). The main role of S-100 is to influence the cell answer by Ca signal transduction: it initiates a signal, influences its strenght, regulates cell response, binds with protein p53 and thus defines cell differentiation and motility.

The presence of S-100 is associated with definite diseases: S-100 A8 works as a hemotactic factor, S-100 B is connected with melanoma, Alzheimer's disease, Down's syndrome, epilepsia (4, 9).

S-100 effects depend on its concentration: at low concentrations it works as a growth and differentiation factor, and at higher concentrations it induces apoptosis. S-100 is used mainly as a melanoma marker (7, 8).

There are no literature data regarding its relation to eye melanoma.

MATERIALS AND METHODS

We determined S-100 protein using the ELISA (Sangtec) and hemiluminiscence methods (Elecsys, Roche). We analyzed 10 donors to check their cut-off level and 21 patients (7 men and 14 women) with eye melanoma. The diagnosis was confirmed by histological examination of operation material. In 2004, the Sangtec company changed the method, and therefore during the first observation the cutoff level was 0.124 $\mu\text{g/l}$, but since 2004 it rose up to 91 ng/l (7).

The average age of donors was 36 years and of eye melanoma patients 47 years (range, 27-65 years).

The hemiluminiscence method Elecsys (Roche) was used in the observation of cutaneous melanoma patients; the cut-off level obtained from 206 appa-

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rently healthy volunteers was 105 pg/ml (Roche). Fifty-seven cutaneous malignant melanoma patients at various stages of disease were examined for protein S-100 under follow-up examination; 38 patients had no evidence of disease (NED), 12 patients had lymph node metastases, and 7 patients had visceral or/and distant skin metastases.

The average age of the examined group was 50 years (range, 24–76). There were 18 men and 39 women.

RESULTS

We examined 10 healthy volunteers. The obtained results are shown in Fig. 1.



Fig. 1. S-100 level in healthy volunteers and Sangtec company

We obtained the results that are below the producing company results. The average S-100 level in eye melanoma patients is shown in Fig. 2.

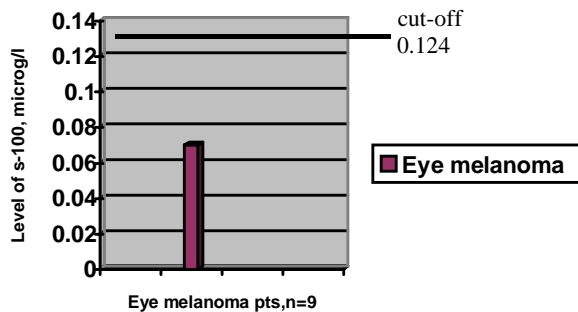


Fig. 2. S-100 level in eye melanoma patients

In 2004 Santag changed the method, so the S-100 cut-off level 25–91 ng/l has been used since 2004. Figure 3 shows the average level of S-100 in eye melanoma patients.

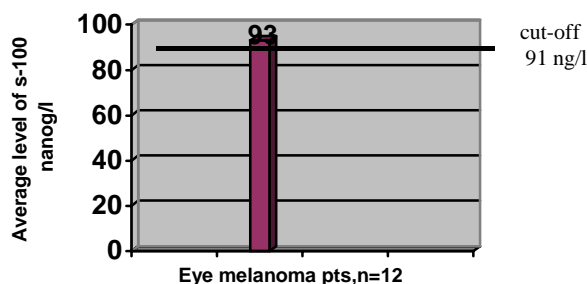


Fig. 3. Average S-100 level in eye melanoma patients

In 32% of eye melanoma patients the S-100 level was elevated.

Some examples. Patient X with the first-time diagnosed eye melanoma showed S-100 level 70 ng/l before treatment. After a radiotherapy cycle the patient had the S-100 level of 30 ng/l; the process progressed, and before surgery (enucleation) the S-100 level was 70 ng/l. In this case the cutoff level was not exceeded.

Another patient, Y, had the S-100 level 60 ng/l; after six months the level was 100 ng/l and a progression was observed.

The results obtained in malignant cutaneous melanoma are shown in Table 1.

Table 1. S-100 protein level in cutaneous melanoma patients

Group	n	S-100 protein level, pg/ml
NED	38	55.7 ± 28.2
Lymph node metastases	12	96.3 ± 36.0

The group of patients with visceral metastases or/and distant skin metastases had S-100 levels from 70.4 pg/ml to 8042 pg/ml. The level depended on the site and number of metastases; six of them had S-100 concentration above the cut-off level. Only one patient had a normal S-100 protein level: he had cutaneous melanoma with lymph node metastases and eye melanoma. Thus, patients with a more advanced disease had higher average S-100 protein levels; 52% of patients with distant metastases had elevated S-100 levels.

DISCUSSION

S-100 level was elevated in 1/3 of patients with eye melanoma. We suggest that these patients need more serious examination to exclude the presence of metastases.

Some authors (6, 7) have shown S-100 specificity to be 99% and sensitivity 47% in cutaneous melanoma, sensitivity depending on the stage of the disease: sensitivity was 21% in stage III and 79% in stage IV.

Other investigators (6–9) show that 85% of patients with metastatic melanoma have their S-100 level above the cutoff. If the elevation of S-100 level happened before starting any therapy, the average survival was 12 years.

We observed elevated S-100 protein levels in 52% of patients with cutaneous melanoma and distant metastases. Six patients had high levels, some of them higher than 6000–8000 pg/ml. We suggest S-100 level to be higher in those who have an advanced disease with multiple metastases or metastases to other sites. Only 4 of 12

patients with lymph node metastases had elevated S-100 protein levels. Those patients may have an occult disease and thus need more frequent examination.

S-100 protein is shown to be one of the best contemporary markers in melanoma patients. As mentioned above, there are no literature data on the relation of S-100 to eye melanoma. In our investigation, we observed that we could use our own cutoff level, too, but the control group was small, therefore we preferred the company-defined cutoff.

In skin melanoma, the specificity was 99% and sensitivity 47% (6–8). In stage III, the sensitivity was 21%, but in stage IV 79% (6, 7). We obtained a 42% sensitivity in eye melanoma.

85% of patients with metastatic melanoma had elevated S-100 levels. If the increase of S-100 level happened before any therapy, the average survival was 7 months. If the cutoff level was not exceeded, the average survival was 12 years.

CONCLUSIONS

1. S-100 protein levels were elevated in 32% of eye melanoma patients and 52% of cutaneous melanoma patients.

2. S-100 protein is more sensitive in cutaneous malignant melanoma, and elevation of its level or high S-100 protein levels are indicative of a more unfavourable prognosis.

3. S-100 could be used as a marker in eye melanoma.

4. Our results are preliminary for eye melanoma, and we have to enlarge the group of examined patients.

5. An individual S-100 protein level must be taken into account to evaluate changes in the course of dis-

ease. S-100 is used as a marker of an extensive disease and for observation of disease therapy effect.

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