

## Short report

# Prognostic significance of serum $\alpha_1$ -acid glycoprotein in patients with glioblastoma multiforme: a preliminary communication

HIROSHI MATSUURA, SHOZO NAKAZAWA

*From the Department of Neurosurgery, Nippon Medical School, Tokyo, Japan*

**SUMMARY** The relationship between the levels of serum acute phase reactant proteins ( $\alpha_1$ -acid glycoprotein,  $\alpha_1$ -antitrypsin, haptoglobin) was investigated in patients with glioblastoma multiforme in relation to their prognosis.  $\alpha_1$ -acid glycoprotein was higher in the patients who died within one year after admission than in those with a longer survival time. It is suggested that serum  $\alpha_1$ -acid glycoprotein profiles provide prognostic information in patients with glioblastoma multiforme.

Serum acute phase reactant proteins (APRPs) increase in cancer patients as well as in those with acute and chronic inflammation, trauma and autoimmune diseases.<sup>1-3</sup> Since the levels of APRPs correlate closely with the extent of disease, it appears that these proteins have immunological properties which affect a host's defences against tumours.<sup>4-8</sup> However, there have been few studies on APRPs in patients with brain tumours,<sup>9</sup> and no reports concerning the relationship between the serum concentration of APRPs and the spread of disease or the host's immunological competence.

To investigate the relationship between the serum concentration of APRPs in glioma patients and the host-tumour response, we measured several APRPs in addition to performing the purified protein derivative (PPD) skin test.

### Subjects and methods

Sixteen patients (8 males and 8 females) with glioblastoma multiforme were studied, aged from 20 to 66 years. They had no concomitant disease and were diagnosed on the basis of the histological findings after surgery. Nine healthy

volunteers with age and sex distributions similar to those of the patients were used as controls. Blood specimens were collected by peripheral venipuncture prior to treatment. The determination of  $\alpha_1$ -acid glycoprotein,  $\alpha_1$ -antitrypsin and haptoglobin was by the single radial immunodiffusion method (Hoechst Japan Co, Tokyo). The PPD skin test was performed prior to treatment to evaluate the cellular immune competence of the patients. PPD (0.05  $\mu$ g/0.1 ml) was injected subcutaneously into the forearm, and the flare reaction of the skin was examined 48 hours later. Erythema of more than 10 mm in diameter with a distinct indurated margin was regarded as positive. All patients were treated with surgical operation (subtotal removal of the tumour), anticancer drugs (ACNU 100 mg, vincristine 1 mg) and radiation (5000 rads).

The patients were divided evenly into two groups. Those who died within one year after the time of determination of the APRPs and PPD skin test (Group 1), and those who survived more than one year (Group 2). The APRP levels and PPD skin test results were compared between these two groups, and the data were analysed by Student's *t* test.

### Results

Elevated levels of  $\alpha_1$ -acid glycoprotein,  $\alpha_1$ -antitrypsin and haptoglobin were seen in the patients compared with the normal controls (table). As shown in the figure, the  $\alpha_1$ -acid glycoprotein level was higher in Group 1 than in Group 2. The  $\alpha_1$ -antitrypsin and haptoglobin levels were higher in Group 1, but not significantly. The PPD skin test was negative in seven out of eight cases in Group 1

Address for reprint requests: Dr Hiroshi Matsuura, Department of Neurosurgery, Nippon Medical School, 1-1-5, Sendagi, Bunkyo-ku, Tokyo 113, Japan.

Received 6 November 1984  
Accepted 2 February 1985

Table Serum acute phase reactant proteins in normal controls and patients with glioblastoma multiforme (mg/dl)

	$\alpha_1$ -acid glycoprotein	Haptoglobin	$\alpha_1$ -antitrypsin
Normal controls (N = 9)	57.2 $\pm$ 3.1 (Mean $\pm$ SE)	111.5 $\pm$ 19.5	197.2 $\pm$ 6.1
Patients with glioblastoma multiforme (N = 16)	108.8 $\pm$ 10.4*	270.7 $\pm$ 39.2*	315.8 $\pm$ 32.1*

\*Significantly different from normal controls ( $p < 0.05$ ).

and two out of eight cases in Group 2. The normal controls were all positive.

### Discussion

Cellular immunity is known to be suppressed in patients with advanced cancer. One of the causes of this suppressed immunity is existence of humoral immunosuppressive factors in the serum. *In vivo* and *in vitro* studies have demonstrated that APRPs suppress the lymphocyte proliferation response to antigens or mitogens.<sup>10-14</sup>

APRPs are produced in the liver and increase in response to various types of diseases. Since the Kupffer cells digest various antigens in the blood, the production of APRPs may be closely related to liver function as the reticulo-endothelial system.<sup>15</sup> On the other hand, there is evidence that these proteins can be synthesised in lymphocytes and tumours.<sup>16-18</sup>

Our present study confirmed that there is a statistically significant increase in  $\alpha_1$ -acid glycoprotein,  $\alpha_1$ -antitrypsin and haptoglobin in the serum of patients with glioblastoma multiforme. These results agree with those for APRPs in patients with cancers of other organs.

It is known that patients with malignant brain tumours have impaired cellular immunity, as do patients with cancers of other organs.<sup>19</sup> The PPD skin test is one of the simplest and most reliable examinations to evaluate cellular immunity in patients with malignant tumours in Japan because most adult Japanese have been sensitised to the tubercle bacilli. The results of this test are closely related to the extent of tumours and prognosis in such patients.<sup>20</sup>

In the present study, most of the patients in Group 1 whose prognosis was poor revealed negative PPD skin reaction and higher levels of  $\alpha_1$ -acid glycoprotein compared to those in Group 2. The data suggest that the immunosuppressive activity in patients with glioblastoma multiforme is due to at least in part to the increase in  $\alpha_1$ -acid glycoprotein. Thus, in addition to such parameters of cellular immune competence as the PPD skin test, determination of the serum  $\alpha_1$ -acid glycoprotein level in these patients may also be useful in evaluating the prognosis.

### References

- Cooper EH, Turner R, Geekie A, *et al.* Alphaglobulins in the surveillance of colorectal carcinoma. *Biomedicine* 1976;24:171-8.
- Harris CC, Primack A, Cohen MH. Elevated  $\alpha_1$ -antitrypsin levels in lung cancer patients. *Cancer* 1974;34:280-1.
- Mueller WK, Handschumacher R, Wade ME. Serum haptoglobin in patients with ovarian malignancies. *Obstet Gynaecol* 1971;38:427-35.
- Bastable JRG, Richards B, Haworth S, Cooper EH.

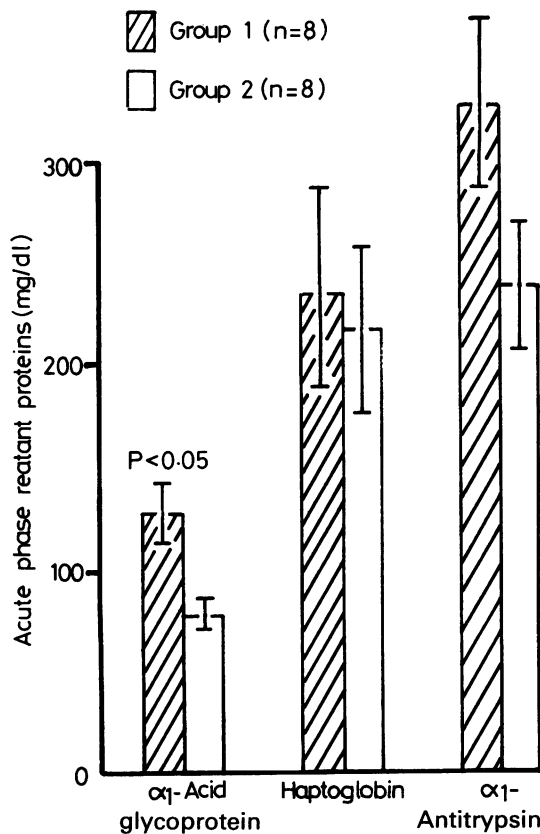


Fig Comparison of acute phase reactant proteins in patients with glioblastoma multiforme.

- Acute phase reactant proteins in the clinical management of bladder cancer. *Br J Urol* 1979;51:283-9.
- <sup>5</sup> Latner AL, Tumer GA, Lamin MM. Plasma alpha-1-antitrypsin levels in early and late carcinoma of the cervix. *Oncology* 1976;33:12-4.
- <sup>6</sup> Roberts JG, Keyser JW, Baum M. Serum  $\alpha_1$ -acid glycoprotein as an index of dissemination in breast cancer. *Br J Surg* 1975;62:816-9.
- <sup>7</sup> Velde ER, Berrens L, Zegers BMJ, Ballieux RE. Acute phase reactants and complement components as indicators of recurrence in human cervical cancer. *Eur J Cancer* 1979;15:893-9.
- <sup>8</sup> Ward AM, Cooper EH, Houghton AL. Acute phase reactant proteins in prostatic cancer. *Br J Urol* 1977;49:411-8.
- <sup>9</sup> Weiss JF, Morantz RA, Bradley WP, Chretien PB. Serum acute phase proteins and immunoglobulins in patients with gliomas. *Cancer Res* 1979;39:542-4.
- <sup>10</sup> Baskies AM, Chretien PB, Weiss JF, et al. Serum glycoproteins in cancer patients: first report of correlation with in vitro and in vivo parameters of cellular immunity. *Cancer* 1980;45:3050-60.
- <sup>11</sup> Chiu KM, Mortensen RF, Osmond AP, Gewurtz H. Interactions of  $\alpha_1$ -acid glycoproteins with the immune system. I. Purification and effect upon lymphocyte responsiveness. *Immunology* 1977;32:997-1005.
- <sup>12</sup> Larsen B, Heror I, Thorling EB. Elevated Serum Cu in Hodgkin's disease and inhibitory effects of ceruloplasmin on lymphocyte response in vitro. *Eur J Cancer* 1980;16:415-21.
- <sup>13</sup> Mortensen RF, Gewurtz H. Effects of C-reactive protein on the lymphoid system: Inhibition of mixed lymphocyte reactivity and generation of cytotoxic lymphocytes. *J Immunol* 1976;116:1244-50.
- <sup>14</sup> Samak R, Edelstein R, Israel L. Immunosuppressive effect of acute-phase reactant proteins in vitro and its relevance to cancer. *Cancer Immunol Immunother* 1982;13:38-43.
- <sup>15</sup> Appfel CA, Peters JH. Tumors and serum glycoproteins. The "symbodies". *Progr Exp Tumor Res* 1969;12:1-54.
- <sup>16</sup> Gahmberg CG, Andersson LC. Leukocyte surface origin of human  $\alpha_1$ -acid glycoprotein (orosomuroid). *J Exp Med* 1978;148:507-21.
- <sup>17</sup> Lipsky JJ, Berninger RW, Hyman LR, Talamo RC. Presence of alpha-1 antitrypsin on mitogen-stimulated human lymphocytes. *J Immunol* 1979;122:24-6.
- <sup>18</sup> Yoshimura S, Tamaoki N, Ueyama Y, Hata J. Plasma protein production by human tumors xenotransplanted in nude mice. *Cancer Res* 1978;38:3474-8.
- <sup>19</sup> Brooks WH, Caldwell HD, Mortara RH. Immune responses in patients with gliomas. *Surg Neurol* 1974;2:419-23.
- <sup>20</sup> Iwamori S, Nagata N, Ishii T, Hamai Y, Oya M, Murakami K. Follow-up PPD skin test in cancer patients. *Clin Immunol (Tokyo)* 1970;1:704-14. (Jpn)