

Serum IgE levels in neurofibromatosis 1

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Summary

A descriptive case study was performed on 75 patients with NF1 (neurofibromatosis type 1) from the CNNF (Brazil) database. Serum IgE levels were determined using the IgE radioimmunosorbent test, with the reference values of 75–502 IU mL⁻¹. The patients were divided into groups, with 25 patients presenting plexiform neurofibromas, 25 presenting neurofibromas and 25 presenting no neurofibromas. The purposes of this study were to determine the serum IgE levels of patients with NF1 presenting plexiform neurofibromas, neurofibromas and no neurofibromas, as well as to determine possible correlations between serum IgE levels and the size of the plexiform neurofibromas and neurofibromas presented by these patients. Elevated serum IgE levels were observed in all the patient groups. We did not observe a correlation between IgE levels and age in these patients; however, we did observe correlations between IgE levels and neurofibroma and plexiform neurofibroma size. We suggest further studies to confirm these results and to investigate in greater depth the possible role of IgE in the development and growth of neurofibromas and plexiform neurofibromas in NF1.

Introduction

Neurofibromatosis type 1 (NF1) or von Recklinghausen disease is an autosomal dominant disorder occurring in roughly 1 : 2500 births (Riccardi, 1981). A neurocutaneous syndrome, NF1 may affect multiple organs and systems, and patients with NF1 may present a variety of symptoms and degrees of severity, ranging from café au lait spots to neurofibromas to plexiform neurofibromas (Friedman *et al.*, 1999; Rubenstein & Korf, 2005).

NF1 primarily affects cells involved in the growth of nerve tissue, and may cause tumours, which frequently grow on the peripheral nerves, on any location of the

body and at any age (Geller & Bonalumi Filho, 2004). Some manifestations are progressive and may result in morbidity and mortality, although the majority of patients with NF1 are able to carry out normal activities (Geller & Bonalumi Filho, 2004; Rubenstein & Korf, 2005).

The diagnosis of NF1 depends on the presence of two or more diagnostic criteria, including six or more café au lait spots, two or more neurofibromas or one or more plexiform neurofibromas, inguinal or axillary freckling, optic glioma, two or more Lisch nodules, a distinctive osseous lesion such as sphenoid dysplasia or thinning of long-bone cortex with or without pseudoarthrosis, a first-degree relative diagnosed with NF1 based on the previous criteria (Riccardi, 1987; Davis, 1997; Friedman *et al.*, 1999; Geller & Bonalumi Filho, 2004; Rubenstein & Korf, 2005).

Neurofibromas are the most common benign tumours found in patients with NF1, and are formed by the proliferation of the cellular components of the peripheral nerve sheath (Waggoner *et al.*, 2000). Neurofibromas are composed of Schwann cells, fibroblasts, perineurial cells and mast cells (Friedman *et al.*, 1999). Among patients with NF1, neurofibromas are present in 94% of adults above 30 years of age (Geller & Bonalumi Filho, 2004). Some authors have suggested an increase in the number of neurofibromas during puberty and pregnancy, indicating a possible hormonal involvement in the development of neurofibromas (Dugoff & Sujansky, 1996; Geller & Bonalumi Filho, 2004).

Plexiform neurofibromas are characterized by unpredictable growth patterns and are composed of multiple cell types (Friedman *et al.*, 1999). Plexiform neurofibromas are classified as benign peripheral nerve sheath tumours. They are not metastatic, but are highly vascularized (Geller & Bonalumi Filho, 2004). Although the growth pattern of plexiform neurofibromas is slow, they can be locally invasive and present with periods of accelerated growth, especially during childhood and adolescence. Plexiform neurofibromas can be present at birth and can appear at any age in patients with NF1 (North, 1998; Korf, 1999).

Immunoglobulin E (IgE) levels have been shown to be elevated in various parasitic infections, suggesting that IgE antibodies are indirectly responsible for the elimination of parasites through the liberation of vasoactive substances as the result of mast-cell degranulation (Arbesman *et al.*, 1972; Cueva & Navarro, 1973; Radermecker *et al.*, 1974; Bezjak, 1975; Ottsen *et al.*, 1979; Grove, 1980).

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A potential link between cancer and the immune system, particularly IgE, has been investigated by numerous researchers, with varied results (Winters & Heiner, 1976; Blondal & Nou, 1981; Ownby *et al.*, 1982; Berczi *et al.*, 1983; Jankovic *et al.*, 1985; Levo *et al.*, 1985; Vijayakumar *et al.*, 1986; Lal *et al.*, 1988; Eckschlager *et al.*, 2004; Wiemels *et al.*, 2004). However, there has been little or no research on the role of IgE in the pathogenesis and development of neurofibromatosis, particularly in neurofibromas and plexiform neurofibromas.

In this study, we observed the serum IgE levels of 75 patients with NF1, 25 of which presented plexiform neurofibromas, 25 presenting neurofibromas, and 25 patients with no signs of neurofibromas or plexiform neurofibromas.

The purpose of this study was to observe and compare the serum IgE levels of these patients with NF1, and, in the case of the patients presenting neurofibromas and plexiform neurofibromas, to determine a possible correlation between serum IgE levels and the size of the neurofibromas and plexiform neurofibromas presented by these patients.

To our knowledge, this is the first study of serum IgE levels in NF1.

Materials and methods

We performed a descriptive case study on 75 patients with NF1 registered in the database of the Centro Nacional de Neurofibromatose (CNNF — Brazil), a national reference center for NF. Twenty-five patients were selected for each group among patients in the database presenting plexiform neurofibromas (N1 group), neurofibromas (N2 group), and no neurofibromas or plexiform neurofibromas (N3 group). Because of the smaller number of patients presenting plexiform neurofibromas in the database, we first randomly selected 25 patients with plexiform neurofibromas from the database. Following this selection, the two remaining groups were filled.

We tried to maintain homogeneity between the three patient groups, based on the sex and age distribution. With regard to the age range, we established a margin of variation of up to 6 months, using the month of birth as a reference. Initially, we tried to identify patients for the N2 and N3 groups of the same sex, born on the same month and year. When these were not found, we searched for patients born 1 month earlier or later, and so on, until

the group size was completed. In each age range, we selected a number proportional to the total size of the group in the CNNF database.

The size (mm) of the largest neurofibroma and plexiform neurofibroma presented by each patient was recorded in the clinical form. Serum IgE levels were evaluated using the Phadebas IgE radioimmunosorbent test, with the reference values of 75–502 IU mL⁻¹, in accordance with the procedures used by the laboratory. Low serum IgE levels were defined as < 75 IU mL⁻¹; normal levels were defined as 75–502 IU mL⁻¹; elevated serum IgE levels were defined as > 502 IU mL⁻¹. The serum samples used had been obtained during previous visits for clinical follow-up of the patients at the CNNF.

The inclusion criteria in this study required patients to be diagnosed with NF1 and registered with the CNNF, with a stored serum sample from a previous visit, and who were willing to sign an informed consent. The exclusion criteria included clinical presentation of allergy, autoimmune disorders, atopic dermatitis, history of asthma or rhinitis, malnutrition and parasitosis, as these conditions may alter serum IgE levels. A careful review of each patient's medical history was performed using the information stored in the CNNF database.

In order to verify correlation between the variables, we used the Pearson correlation test (R^2). To verify differences between averages we used the variance analysis. The heterogeneity between the patient groups was verified through the heterogeneity chi-squared test (χ^2).

Results

The distribution of the subcutaneous, cutaneous and pedunculated neurofibromas was homogenous between the N1 and N2 patient groups ($\chi^2 = 0.85$; $P > 0.05$; d.f. = 2). The mean sizes of the total neurofibromas observed was also homogenous between the two groups ($\chi^2 = 1.85$; $P > 0.05$; d.f. = 2). The demographic data of the patients included in this study are summarized in Table 1.

The mean size of the subcutaneous neurofibromas was larger in the N1 group than in the N2 group (F statistic = 11.73; $P = 0.001919$). There was no variance in the size of the cutaneous neurofibromas (F statistic = 0.49; $P > 0.05$) and pedunculated neurofibromas (F statistic = 0.00; $P > 0.05$) between the N1 and N2 groups.

Table 1. Demographic characteristics

Characteristic	N1 group	N2 group	N3 group	Total
<i>n</i>	25	25	25	75
Sex				
Male	13	10	11	34
Female	12	15	14	41
Age (Years)	25 (± 12.68)	18.04 (± 13.37)	12.4 (± 5.07)	18.48 (± 11.4)
Male	24.53 (± 8.87)	26 (± 15.9)	10.54 (± 5.22)	20.44 (± 12.43)
Female	25.5 (± 12.68)	12.73 (± 8.27)	13.85 (± 4.62)	16.85 (± 10.34)

Data are *n* or means ± SD.

Table 2. Serum IgE levels in the patient groups

Patients (n)	Low	Normal	Elevated
Total	3	50	22
Male	2	20	12
Female	1	30	10
N1 group	0	15	10
Male	0	6	7
Female	0	9	3
N2 group	1	17	7
Male	1	7	2
Female	0	10	5
N3 group	2	18	5
Male	1	7	3
Female	1	11	2

Most of the patients of both sexes presented IgE levels within the range of normal (Table 2). Elevated serum IgE levels were observed in all three patient groups, and were most frequently observed in the N1 patient group. Low serum IgE levels were most frequently observed in the N3 group.

We did not observe a correlation between age and serum IgE levels in all of the patients ($R^2 = 0.0115$), or in the female ($R^2 = 0.0019$) and male patients ($R^2 = 0.0428$). In the N1 group, we did not observe a correlation between age and IgE levels ($R^2 = 0.0046$), and in the male and female patients of this group, we also did not observe a correlation ($R^2 = 0.0309$, and $R^2 = 4E-05$, respectively). No correlation was observed between age and serum IgE level in the total patients of the N2 group ($R^2 = 0.0014$), in the female ($R^2 = 0.0661$) and male ($R^2 = 0.0661$) patients of this group. In the N3 group, we did not observe a correlation between age and serum IgE levels in all of the patients ($R^2 = 0.0161$), or in the female ($R^2 = 0.1339$) and male patients ($R^2 = 0.0069$).

None of the patients among the N1 and N2 groups presenting subcutaneous and internal plexiform neurofibromas and subcutaneous neurofibromas presented low serum IgE levels. The IgE levels of the majority of the patients presenting subcutaneous and cutaneous neurofibromas and subcutaneous plexiform neurofibromas were within the normal range. However, in the patients presenting pedunculated neurofibromas, we observed an equal number of individuals with elevated serum and normal serum IgE levels. Low IgE levels were observed in patients presenting cutaneous and pedunculated neurofibromas.

We did not observe a correlation between the size (mm) of the subcutaneous neurofibromas ($R^2 = 0.0021$), the cutaneous neurofibromas ($R^2 = 0.1718$), or the subcutaneous plexiform neurofibromas ($R^2 = 0.0028$) and the serum IgE levels in all of the N1 and N2 patients. However, we did observe a correlation between the size of the pedunculated neurofibroma in relation to the increase in IgE levels ($R^2 = 0.4426$).

In the female patients, we did not observe a correlation between serum IgE levels and the size of the subcutaneous neurofibromas ($R^2 = 0.1457$), or the size of the cutaneous

neurofibromas and the serum IgE levels of these patients ($R^2 = 0.057$).

In the male patients, we did not observe a correlation between the size of the subcutaneous neurofibromas and the serum IgE levels ($R^2 = 0.1095$). However, we did observe a correlation between cutaneous neurofibroma size and an increase in serum IgE levels ($R^2 = 0.3825$).

In the patients of the N1 group, we observed a correlation between the size of the subcutaneous neurofibromas and an increase in serum IgE levels ($R^2 = 0.4012$). We did not observe a correlation between the size of the cutaneous neurofibromas and IgE levels in this group ($R^2 = 0.1872$). No correlation between subcutaneous plexiform neurofibroma size and serum IgE levels was observed ($R^2 = 0.0028$).

In the female patients of the N1 group, we did not observe a correlation between subcutaneous neurofibroma size and serum IgE levels ($R^2 = 0.1466$). The cutaneous neurofibromas observed in these patients showed no correlation to serum IgE levels ($R^2 = 0.0991$), neither did the subcutaneous plexiform neurofibromas ($R^2 = 0.0093$).

In the male patients of the N1 group, we observed a correlation between the size of the cutaneous neurofibromas and the increase in serum IgE levels ($R^2 = 0.4455$). We did not observe a correlation between the size of the subcutaneous plexiform neurofibromas and the serum IgE levels in these patients ($R^2 = 0.0515$).

In the N2 group, we did not observe a correlation between serum IgE levels and the size of the subcutaneous neurofibromas ($R^2 = 0.1612$), or the size of the cutaneous neurofibromas ($R^2 = 0.1683$).

In the female patients of the N2 group, we did not observe a correlation between serum IgE levels and the size of the cutaneous neurofibromas ($R^2 = 0.0371$), or the subcutaneous neurofibroma size ($R^2 = 0.0329$).

In the male patients of this group, we observed a correlation between a decrease in the size of the subcutaneous neurofibromas and elevation of serum IgE levels ($R^2 = 0.4923$). This result may be due to the small sample size, as there was only one individual presenting elevated IgE levels, who also presented a small subcutaneous neurofibroma. In this group, we also observed a correlation between cutaneous neurofibroma size and elevation of serum IgE levels ($R^2 = 0.5849$).

Discussion

In the literature reviewed, we did not identify studies determining serum IgE levels in neurofibromatosis. In this study, in all of the patients, we did not observe a correlation between serum IgE levels and age. However, we did observe a tendency of increase in IgE levels correlated to the size of pedunculated neurofibromas. In the male patients, we also observed a tendency of elevation of serum IgE levels correlated with an increase in the size of the cutaneous neurofibromas. These correlations were not observed in the female patients. In the male patients, we also observed a correlation between elevated IgE levels

and the presence of pedunculated and internal and subcutaneous plexiform neurofibromas.

In the N1 patient group, we observed a tendency of elevated serum IgE levels correlated with the increase in the size of the subcutaneous neurofibromas. In the male patients of this group, we also observed a tendency of increase in cutaneous neurofibroma size correlated with increased serum IgE levels. The male patients in the N1 group presented a tendency of elevated IgE, which was not observed in the other groups (female N1 patients, N2 and N3 groups).

In the male patients from the N2 group, we observed a tendency of increase in IgE levels correlated with an increase in the size of the cutaneous neurofibromas. In this group, we also observed a tendency of IgE elevation correlated with a reduction in subcutaneous neurofibroma size. This tendency was not observed in any of the other groups, and we do not have a hypothetical explanation for this finding, other than the sample size, as mentioned previously.

While further studies are suggested to confirm these results, in the patients presenting plexiform neurofibromas and neurofibromas, we observed that at least 20% of the patients in the respective groups and subgroups presented elevated IgE levels. Although the literature does not contain descriptive information regarding serum IgE levels correlated to sex, age and neurofibroma size in neurofibromatosis, we are able to glean from the literature certain abstractions that enable us to gain a greater understanding of the above results.

The serum IgE levels of normal Brazilian patients have been identified in previous studies as being higher than those described for normal North American and European populations. One possible explanation for this fact lies in previous helminthic exposures in normal Brazilian controls (Geller & Geller, 2000).

At the time this study began, none of the patients presented malignancy. However, two female patients from the N1 group, both of whom presented elevated serum IgE levels, showed signs of malignant transformation during later follow-up visits.

At the time of the submission of this study for publication, no additional patients had presented malignant transformations. Previous studies have demonstrated that elevated serum IgE levels may be an indicator or prognostic marker of malignancy.

Elevated serum IgE levels as prognostic indicators of malignancy have been suggested for breast cancers, carcinomas of the oral cavity, cervix and uterus, as well as bronchial carcinomas, compared to a control population (Blondal & Nou, 1981; Ownby *et al.*, 1982; Jankovic *et al.*, 1985; Vijayakumar *et al.*, 1986 Lal *et al.*, 1988). IgE tumour antibodies have been found in the plasma of gastrointestinal carcinoma patients, which decreased or disappeared after surgical treatment (Berczi *et al.*, 1983). Elevated serum IgE levels have also been found in Hodgkin's disease patients (Wiemels *et al.*, 2004). Some authors have suggested an increase in serum IgE levels correlated with the stage of the cancer. However, in the case of some

cancers such as optic gliomas, an inverse relation has been observed, with a reduction in IgE levels in optic glioma patients as compared to normal controls. In other cases, investigators did not observe any correlation between serum IgE levels and solid tumours, as well as carcinomas of the breast and colon (Winters & Heiner, 1976; Levo *et al.*, 1985).

Evidence of elevated serum IgE levels in the presence of cancer has led to a suggestion of the involvement of IgE in antitumour immunity. Reali *et al.* (2001) suggested that IgE antibodies trigger an allergic response at the tumour site by the recruitment and activation of effectors carrying FcεRI, such as eosinophils, thus favouring the destruction of the tumour cell. Other possible roles of IgE in tumorigenesis have been suggested, such as the role of IgE in the stimulation of mast cells, which have been implicated in the tumour development process through angiogenesis (Boesiger *et al.*, 1995; Abe *et al.*, 2000; Sawatsubashi *et al.*, 2000; Toth-Jakatics *et al.*, 2000; Feoktistov *et al.*, 2003). It should, however, be noted that non-degranulated mast cells also take part in tumour growth (Theoharides & Conti, 2004).

However, this brings us to the question of the IgE levels below the normal range ($< 75 \text{ UI mL}^{-1}$), observed in three of the patients in this study, one patient in the N2 group and two patients in the N3 group. We consider the hypothesis of an infectious process, likely a viral infection, which would have resulted in transitory hypogammaglobulinemia E (Adkinson *et al.*, 2003). In light of the limitations drawn by the study design, this hypothesis must be evaluated through new clinical observations of these patients.

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References

- Abe, M., Kurosawa, M., Igarashi, Y., Ishikawa, O. & Miyachi, Y. (2000) Influence of IgE-mediated activation of cultured human mast cells on proliferation and type I collagen production by human dermal fibroblasts. *Journal of Allergy and Clinical Immunology*, **106**, S72–S77.
- Adkinson, N.F., Yunginger, J.W., Buse, W.W., Bochner, B.S., Holgate, S.T. & Simons, F.E.R., eds. (2003) *Middleton's Allergy: Principles and Practice*. vols 1 and 2. 6th edn. Mosby, St. Louis, MO.
- Arbesman, C.E., Ito, K., Wypych, J.I. & Wicher, K. (1972) Measurement of serum IgE by a one-step single radiodiffusion method. *Journal of Allergy and Clinical Immunology*, **49**, 72.
- Berczi, I., Holford-Strevans, V., Warsi, Z.H., McMorris, L.S., Thorlakson, R.H., Thorlakson, T.K. & Schon, A.H. (1983) Tumor-reactive IgE antibodies in plasma of patients with gastrointestinal carcinomas. *Cancer Immunology, Immunotherapy*, **14**, 180.

- Bezjak, B. (1975) Immunoglobulin studies in strongyloidiasis with special reference to raised IgE levels. Preliminary communication. *American Journal of Tropical Medicine and Hygiene*, **24**, 945.
- Blondal, T. & Nou, E. (1981) Circulating IgE levels in patients with bronchial carcinomas. *British Journal of Diseases of the Chest*, **75**, 77.
- Boesiger, J., Tsai, M., Maurer, M., Yamaguchi, M., Brown, L.F., Claffey, K.P., Dvorak, H.F. & Galli, S.J. (1995) Mast cells can secrete vascular permeability factor / vascular endothelial growth factor and exhibit enhanced release after immunoglobulin E-dependent upregulation of Fc ϵ receptor I expression. *American Journal of Pathology*, **147**, 564.
- Cueva, V.J. & Navarro, Q.F.B.B.E. (1973) IgE en alérgicos Y parasitados en México. *Alergia*, **21**, 1.
- Davis, R.E. (1997) Review. Diagnosing neurofibromatosis type I in children. *The Nurse Practitioner*, **22**, 79.
- Dugoff, L. & Sujansky, E. (1996) Neurofibromatosis type 1 and pregnancy. *American Journal of Medical Genetics*, **66**, 7.
- Eckschlager, T., Prusa, R., Hladikova, M., Radvanska, J., Slaby, K. & Radvansky, J. (2004) Lymphocyte subpopulations and immunoglobulin levels in Hodgkin's disease survivors. *Neoplasma*, **51**, 261.
- Feoktistov, I., Ryzhov, S., Goldstein, A.E. & Biaggioni, I. (2003) Mast cell-mediated stimulation of angiogenesis. *Circulation Research*, **92**, 485.
- Friedman, J.M., Gutmann, D.H. & MacCollin, M., eds. (1999) *Neurofibromatosis: Phenotype, Natural History, and Pathogenesis*, 3rd edn. Johns Hopkins University Press, Baltimore.
- Geller, M. & Bonalumi Filho, A. (2004). *Neurofibromatose: Clínica, Genética e Terapêutica*, 1st edn. Editora Guanabara Koogan, Rio de Janeiro.
- Geller, M. & Geller, M. (2000) Documentação Brasileira sobre a ausência de elevação da IgE sérica total em infecções por protozoários. *JBM*, **78**, 106.
- Grove, D.I. (1980) Strongyloidiasis in allied ex-prisoners of war in south-east Asia. *British Medical Journal*, **1**, 598.
- Jankovic, D., Bernt, T. & Cepulic, E. (1985) Levels of serum IgE and eosinophilic granulocytes in women with cancer of the uterine cervix. *Jugosl Ginekological Perinatology*, **25**, 61.
- Korf, B. (1999) Plexiform neurofibromas. *American Journal of Medical Genetics (Semin Medical Genetics)*, **89**, 31.
- Lal, H., Singh, B., Wig, U. & Saini, A.S. (1988) Serum immunoglobulin E levels in patients with head and neck cancer. *Journal of Laryngological Otology*, **102**, 432.
- Levo, Y., Wollner, S. & Shalit, M. (1985) Serum IgE levels in patients with cancer. *Annals of Allergy*, **54**, 453.
- North, K.N. (1998) Review. Clinical aspects of neurofibromatosis 1. *European Journal of Paediatric Neurology*, **2**, 223.
- Ottson, E.A., Neva, F.A., Paranjape, R.S., Tripathy, S.P., Thiruvengadam, K.V. & Beaven, M.A. (1979) Specific allergic sensitization to filarial antigens in tropical eosinophilia syndrome. *Lancet*, **1**, 1158.
- Ownby, D.R., Ownby, H.E., Roi, L.D., Howard, L.M., Heppner, G.H. & Brennan, M.J. (1982) Prognostic significance of serum IgE levels in primary breast cancer. *Breast Cancer Research and Treatment*, **2**, 221.
- Radermecker, M., Bekhti, A., Poncelet, E. & Salmon, J. (1974) Serum IgE levels in protozoal and helminthic infections. *International Archives of Allergy*, **47**, 285.
- Real, E., Greiner, J.W., Corti, A., Gould, H.J., Bottazzoli, F., Paganelli, G., Schlom, J. & Siccari, A.G. (2001) IgEs targeted on tumor cells. *Cancer Research*, **61**, 5517.
- Riccardi, V.M. (1981) von Recklinghausen neurofibromatosis. *New England Journal of Medicine*, **305**, 1617.
- Riccardi, V.M. (1987) Neurofibromatosis. *Neurological Clinical*, **5**, 337.
- Rubenstein, A.E. & Korf, B.R. (2005) *Neurofibromatosis: A Handbook for Patients, Families, and Health-Care Professionals*, 2nd edn. Thieme Medical Publishers, New York.
- Sawatsubashi, M., Yamada, T., Fukushima, N., Mizokami, H., Tokunaga, O. & Shin, T. (2000) Association of vascular endothelial growth factor and mast cells with angiogenesis in laryngeal squamous cell carcinoma. *Virchows Archives*, **436**, 243.
- Theoharides, T.C. & Conti, P. (2004) Mast cells: the Jekyll and Hyde of tumor growth. *Trends in Immunology*, **25**, 235.
- Toth-Jakatics, R., Jimi, S., Takebayashi, S. & Kawamoto, N. (2000) Cutaneous malignant melanoma: correlation between neovascularization and peritumor accumulation of mast cells overexpressing vascular endothelial growth factor. *Human Pathology*, **31**, 955.
- Vijayakumar, T., Ankathil, R., Remani, P., Sasidharan, V.K., Vijayan, K.K. & Vasudevan, D.M. (1986) Serum immunoglobulins in patients with carcinoma of the oral cavity, uterine cervix and breast. *Cancer Immunology. Immunotherapy*, **22**, 76.
- Waggoner, D.J., Towbin, J., Gottesman, G. & Gutmann, D.H. (2000) Clinic-based study of plexiform neurofibromas in neurofibromatosis 1. *American Journal of Medical Genetics*, **92**, 132.
- Wiemels, J.L., Wiencke, J.K., Patoka, J., Moghadassi, M., Chew, T., McMillan, A., Miike, R., Barger, G. & Wrensch, M. (2004) Reduced immunoglobulin E and allergy among adults with glioma compared with controls. *Cancer Research*, **64**, 8468.
- Winters, W.D. & Heiner, D.C. (1976) IgE levels in sera of cancer patients. *Journal of Allergy Clinical Immunology*, **57**, 181.