Numerous cases of familial aggregation of Hodgkin’s disease (HD) or non-Hodgkin’s lymphoma (NHL) have been reported. An increased risk of HD in monozygotic twins of HD patients, compared to dizygotic twins has been demonstrated (Mack et al, 1995), providing strong evidence of a genetic susceptibility underlying HD. Among close relatives of patients with NHL, some authors have found that NHL was more frequent than expected by chance (Pottern et al, 1991), whereas others failed to prove this (Haim et al, 1982). NHL in monozygotic twins is a very rare finding which is associated to T phenotype (Schneider et al, 1995).

In June 1995 a 48-year-old male was diagnosed with follicular lymphoma (small cleaved cell), stage IIA, having
infradiaphragmatic lymphadenopathies. He received six courses of CVP (cyclophosphamide 800 mg/m², vincristine 2 mg and prednisone 100 mg for 5 consecutive days), achieving complete remission and then received V-inverted radiotherapy (4500 cGy). He remains in complete remission.

In November 1995 a monozygotic twin of the former was diagnosed with follicular lymphoma (small cleaved cell), stage IVA, with supradiaphragmatic lymphadenopathies and bone marrow involvement. Mononcytosis was established by identical physical appearance, birth history and HLA typing. He received six courses of CHOP (cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², vincristine 2 mg and prednisone 100 mg for 5 consecutive days), achieving partial remission. He was then submitted to intensive chemotherapy with BEAM regimen (carmustine 300 mg/m², etoposide 800 mg/m², cytarabin 800 mg/m² and melphalan 140 mg/m²) and peripheral blood stem cell (PBSC) support. He achieved complete remission but 3 months later presented with a lung adenocarcinoma and subsequently died.

Sections of adenopathies from both patients were stained using the avidin–biotin–peroxidase complex procedure with primary antibodies to CD20, CD3, Bcl-2 and Epstein–Barr virus (EBV) latent membrane protein (LMP-1), demonstrating a strong expression of CD20 and Bcl-2 in lymphomatous cells from both twins (Fig 1). Expression of CD3 and EBV was negative. Immunological markers were also analysed by FacScan flow cytometer on Ficoll-Hipaque isolated cells from an adenopathy from twin 1, showing positive CD19, CD10 and A light chain expression. A PCR amplification at the MBR of the BCL2/IgH translocation was identified in a diagnostic adenopathy from twin 1 (result not shown). DNA extraction from twin 2 samples could not be performed.

The study of NHL cases in close relatives, and specially in monozygotic twins, constitutes a powerful tool for a better understanding of NHL aetiology. Various mechanisms may explain familial association of NHL, including proto-oncogenes expression, tumour suppressor genes inactivation, hereditary immune deficiency disorders, vertical transmission of retroviruses, shared exposure to environmental carcinogens or hereditary impaired ability for their detoxification (Shpilberg et al, 1994). Different factors may act in conjunction. In our case the occurrence of an environmental determinant over a genetic susceptibility is suggested by concordance in time of the two cases. It is possible that this environmental factor could have been a common viral infection, as it is suggested in HD aetiopathogeny (Mack et al, 1995). Our patients had lived together until adulthood, remaining in close contact thereafter. They were non-smokers and had no familial history of haematological neoplasms, immune alterations or contact with carcinogenic agents. A possible role played by an haematological neoplasms, immune alterations or contact with carcinogenic agents. A possible role played by an Epstein-Barr virus (EBV) infection was discarded by EBV immunohistochemistry, which was negative. The demonstration of a rearranged BCL2 gene in twin 1 and overexpression of Bcl-2 protein by immunohistochemistry in both twins suggest that inhibition of apoptosis could be the molecular mechanism implicated in both cases. The presence of an underlying susceptibility to neoplasms in these patients was emphasized by the subsequent presentation of a pulmonary adenocarcinoma in one of the twins.

SERUM M-CSF LEVELS IN KAWASAKI DISEASE

We read with interest the paper by Igarashi et al (1999) describing high serum M-CSF and G-CSF levels in the acute phase of Kawasaki disease (KD). We have reported that massive infiltration of monocytes/macrophages was detected in the coronary artery lesion of KD (Terai et al, 1990). Monocyte chemotactant protein 1, which activates monocytes/macrophages, was also detected in the coronary vascular lesion of acute KD (Terai et al, 1999). Taken together, these results indicate that monocytes/macrophages may play a role in the pathogenesis of KD, especially in the progression of coronary artery lesions. To investigate the involvement of other cytokines, which activate monocytes/macrophages, we also examined the serum M-CSF level in KD and other febrile children.

REFERENCES


Keywords: non-Hodgkin’s lymphoma, monozygotic twins, follicular lymphoma, genetic predisposition, familial aggregation.
The serum level of M-CSF in a total of 51 children was examined in our series. The diagnosis of KD was based on the criteria established in 1984 by the KD Research Committee of Japan. All eight KD patients in our series developed coronary artery aneurysm. The diagnosis of measles was made by their typical clinical courses. RS virus infection and rotavirus infection were diagnosed by detecting the virus-specific antigen from either nasal discharge or stool using an Abbott TEST PAC™ RSV (Abott Laboratories, Tokyo, Japan) or Rota-adeno dry (Orion Diagnostica, Espoo, Finland) respectively. Bacterial infections were diagnosed by isolating pathogens from blood, stool or urine. Those included two upper urinary tract infections, salmonellosis, a pathogenic, vero toxin producing E. coli enterocolitis, and streptococcal bacteraemia. Serum M-CSF was assayed using a Quantikine™ Human M-CSF immunoassay (R & D systems, Minneapolis, Min., U.S.A.).

Our data supported the results of Igarashi et al (1999). Serum M-CSF levels in KD were significantly higher than those in afebrile controls. Although there was no significant difference between the acute and convalescent phase of KD, our results demonstrated a decrease in the serum M-CSF level during the clinical course of KD (Fig 1).

To clarify whether the elevation of serum M-CSF was KD specific, we also examined the acute phase of other febrile diseases in children. Since the number of patients in each disease category was small, it was impossible to perform a statistical analysis. However, Fig 1 demonstrates that high levels of serum M-CSF were observed in the acute phase of measles, RS virus infection, rotavirus infection, bacterial infections, and haemophagocytic syndrome. Further studies are needed to determine the physiological significance of M-CSF in KD.

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Keywords: M-CSF levels, Kawasaki disease.

ELEVATED SERUM LDH IN PATIENTS WITH NON-HODGKIN’S LYMPHOMA: NOT ALWAYS AN OMINOUS SIGN

The serum level of lactate dehydrogenase (LDH) is commonly elevated in lymphoproliferative disorders. In patients with non-Hodgkin’s lymphoma (NHL), LDH values have prognostic value and are commonly used to assess treatment response and monitor for tumour recurrence.

LDH is widely distributed in mammalian tissues, and high concentrations are found in muscle and liver cells in addition to haemopoietic cells and their descendants (Henry, 1996). Because of this distribution, there are other causes of an elevated serum LDH in addition to malignancy. These include myocardial or pulmonary infarction, hepatic dysfunction, haemolysis, and myopathy. Elevated serum LDH levels in association with hypothyroidism have also been reported (Fleisher et al. 1965).
Correspondence

When patients with treated non-Hodgkin’s lymphoma develop other disorders that cause elevated serum LDH levels, anxiety and an unnecessary tumour hunt can result. This may be especially likely with hypothyroidism, which is asymptomatic in its early stages. We report three cases of elevated serum LDH due to hypothyroidism in patients who had been treated for non-Hodgkin’s lymphoma.

Case 1. A 56-year-old man presented in July 1995 with a large-cell lymphoma of the soft tissue of the left neck. Initial serum LDH was 335 U/l (normal 104–236 U/l); serum levels of sensitive thyroid-stimulating hormone (sTSH) and total thyroxine (T4) were normal. The patient received radiation therapy to the left neck and mediastinum and chemotherapy. His serum LDH fell to 249 U/l following treatment, and his free-thyroxine index was normal. 4 months following the completion of treatment, a routine surveillance serum LDH was 469 U/l; on repeat testing it was 493 U/l. Extensive evaluation for recurrent lymphoma was unrevealing. His sTSH was found to be markedly elevated (57.2 mU/l; normal 0.30–5.0 mU/l), and levothyroxine was administered. 6 weeks later the patient’s LDH had fallen to 188 U/l. 5 months later the sTSH and LDH were both within normal limits, and the patient remains free of lymphoma 3 years later. He continues to take levothyroxine daily.

Case 2. A 72-year-old woman presented in April 1990 with a left supraclavicular follicular mixed-cell non-Hodgkin’s lymphoma. Initial serum LDH was normal. She was treated with radiation in a mini-mantle pattern and achieved a clinical complete remission. An intra-abdominal recurrence in 1992 was associated with an LDH of 541 U/l and was successfully treated with chemotherapy. Her LDH fell below 200 U/l. In January 1997 a routine surveillance LDH was found to be 521 U/l. Extensive evaluation for recurrent tumour was unrevealing. Her sTSH was elevated (9.2 mU/l); the T4 level was normal (83 nmol/l; normal 65–160 nmol/l). Her only previous thyroid study had been a normal T4 (87 nmol/l) in 1978. She started levothyroxine therapy. 6 weeks later her LDH had fallen to 125 U/l and her sTSH had normalized at 1.5 mU/l. 2 years later her LDH remains normal and she is lymphoma-free.

Case 3. A 64-year-old woman presented in July 1997 with retroperitoneal large-cell non-Hodgkin’s lymphoma. The serum LDH was 562 U/l. The patient was also found to have an elevated sTSH (12.7 mU/l) with a normal free thyroxine (18 pmol/l; normal 10–24 pmol/l). She began oral levothyroxine. She then received chemotherapy and achieved a complete remission. Following chemotherapy, her sTSH was normal and LDH was 189 U/l. 3 months after completing chemotherapy the patient’s LDH was found to have increased to 273 U/l. Evaluation for tumour recurrence was unrevealing. Her sTSH was checked and elevated (7.6 mU/l), so her levothyroxine dose was increased; 6 weeks later her LDH had fallen to 117 U/l and sTSH was 0.11 mU/l. In August 1998 the patient’s LDH and sTSH were again found to be rising. She admitted to decreasing her levothyroxine dose because of insomnia. She began taking supplementary hog thyroid extract, and her sTSH and LDH returned to normal. Her lymphoma remains in remission.

We report three cases of elevated serum LDH values due to hypothyroidism in patients previously treated for non-Hodgkin’s lymphoma. To our knowledge, no previous cases of LDH elevation due to hypothyroidism in this subgroup of patients have been reported.

In each case, treatment of non-Hodgkin’s lymphoma resulted in normalization of a previously elevated LDH value. Subsequently the LDH was found to be elevated on routine surveillance testing, but no tumour recurrence could then be detected. Biochemical evidence of hypothyroidism was then identified (all three patients were asymptomatic), and the LDH values normalized after thyroid hormone replacement was initiated.

These three cases demonstrate that an elevated serum LDH level may not always be due to tumour recurrence in patients previously treated for non-Hodgkin’s lymphoma. Clinicians must keep the possibility of undiagnosed hypothyroidism in mind, especially in patients previously treated with thyroid radiation, a risk factor for hypothyroidism (Wartofsky, 1998).

REFERENCES


Keywords: LDH, hypothyroidism, non-Hodgkin’s lymphoma, tumour markers, tumour recurrence.

THE FREQUENCY OF THE HAEMOCHROMATOSIS C282Y MUTATION IN THE ETHNIC HUNGARIAN AND ROMANY POPULATIONS OF EASTERN HUNGARY

Hereditary haemochromatosis (HH) represents one of the most common autosomal recessive disorders among Caucasians (1:300), with an estimated carrier frequency of 1 in 8–10 (Edwards et al, 1988). Merryweather-Claire et al (1997) reported data on the global prevalence of putative haemochromatosis mutations and proposed to initiate genetic screening programmes in populations with a high C282Y allele frequency. Most recently a high frequency of
C282Y mutation (allele frequency 5.6, 95% CI 3.6–7.6) was reported for a cohort from Budapest, the capital of Hungary (Tordai et al. 1998). This finding seems to contradict the Celtic origin of the mutation presumed by several authors. However, due to a significant influx of ethnic Germans to the Budapest region during the fifteenth to nineteenth centuries, a population genetic study from this region might not be a true representation of the ethnic Hungarian population. To collect further data on the prevalence of C282Y mutation among ethnic Hungarians we studied a cohort from the eastern part of the country. As to our knowledge no data on the frequency of haemochromatosis C282Y mutation among Romanies have been reported. A Romany population of the same geographic area was also included in the study.

308 randomly selected unrelated healthy ethnic Hungarians (137 males and 171 females) and 140 Romanies (71 males and 69 females) were investigated for the presence of the C282Y mutation. DNA was extracted from peripheral blood buffy coats using QIAamp Blood kit (QIAGEN, Hilden, Germany). Amplification of the segment of the HFE gene containing the C282Y mutation site was performed by using previously described oligoprimers (Feder et al. 1996). The PCR products were digested with Rsa I restriction endonuclease (Sigma, St Louis, Mo.) and the fragments were analysed by electrophoresis in 2% agarose gel.

Table I. The frequency of the haemochromatosis C282Y mutation in eastern Hungary.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Heterozygotes</th>
<th>Homozygotes</th>
<th>Allele frequency (% ± 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hungarians</td>
<td>308</td>
<td>12</td>
<td>2</td>
<td>2.59 ± 1.25</td>
</tr>
<tr>
<td>Romanies</td>
<td>140</td>
<td>1</td>
<td>1</td>
<td>1.07 ± 1.20</td>
</tr>
</tbody>
</table>

The frequency of the C282Y allele among healthy Hungarians (Table I) was below the European average allele frequency (3.8, 95% CI 3.1–4.5) (Merryweather-Clarke et al. 1997) and significantly (P<0.05) below the frequency reported for the Budapest area (allele frequency 5.6, 95% CI 3.6–7.6, Tordai et al. 1998)). Among women the allele frequency for the C282Y mutation was slightly higher than in men, 2.92, 95% CI 1.18–4.70 versus 2.19, 95% CI 1.46–3.92; the difference was not statistically significant. Our results fit well into the south-east to north-west gradient of C282Y allele frequency and do not contradict the theory of the Celtic origin of the mutation.

Romany originate from the Indian subcontinent. They migrated out of India one to two thousand years ago, and the earliest evidence of their arrival in Hungary comes from the fourteenth century (Vekerdi, 1976). The prevalence of the haemochromatosis mutation in the Indian subcontinent is very low (allele frequency 0.2, 95% CI 0.0–0.6) Merryweather-Clarke et al. (1997). In the Romany cohort one heterozygous and one homozygous C282Y mutation were identified. The allele frequency (Table I) was higher than that reported for Asian Indians, but lower than the frequency found among ethnic Hungarians. This finding might reflect a gene influx from the Hungarian ethnic majority. Evidence of such genetic influx has been demonstrated for the blood coagulation factor V Leiden mutation (Balogh et al. 1999).

REFERENCES


Keywords: haemochromatosis, C282Y mutation, Romanies, Hungarians.