HLA-Association in patients with intolerance to mercury and other metals in dental materials

J. Procházková, J. Bártová, E. Ivašková, L. Kupková, I. Šterzl and V.D.M. Stejskal

Institute of Dental Research, Vinohradská 48, 120 60 Prague 2, Czech Republic
IKEM, National HLA Centre, Vídeňská 800, 140 00 Prague 4, Czech Republic
Institute of Endocrinology, Národní 8, 116 94 Prague 1, Czech Republic
Department of Clinical Chemistry, Danderyds Hospital and Karolinska Institute, Stockholm, Sweden

Keywords: HLA antigens, metal intolerance, dental materials

1. Introduction

Metals in the form of biologically active substances are components of various dental materials, including supportive implants. In spite of declared “biocompatibility”, such metals (aluminium, chromium, cobalt, mercury, nickel, platinum, steel, vanadium, and zinc) if present in dental materials, can induce serious local or atopic allergic reactions in sensitive patients [15].

Heavy metals present in dental materials were recognised as responsible for atopic eczema [4], nickel hypersensitivity was related to periodontitis [3] and professional allergy to cobalt chromium dust in dental technicians was described [12]. Potolicchio et al. [8] reviewed data on mechanisms by which metals induce allergic or autoimmune-like reactions and demonstrated that HLA-DP2 molecules do bind cobalt specifically. Therefore prognosis and monitoring of allergic reactions to metal dental materials are theoretically and practically highly relevant.

Diagnostic tests for metal intolerance are fairly restricted. Skin tests are no doubt a diagnostic method for allergies but they also have some disadvantages. These include a possibility that negative skin reactions are not necessarily reliable as the skin might not be always the organ which is metal sensitive. On the other hand, skin reactions might be false positive if the tested materials are highly irritating. About 10 to 20 per cent of persons whose skin tests to the tested allergen is positive do not in fact show any allergic reactions to the given allergen [2,7]. Allergic people can also suffer false negative skin test reactions for reasons which remain unclear [7].

For diagnostic purposes the test system “Memory Lymphocyte Immune Stimulation Assay” (Melisa™, Sweden) is of potential importance. The test is based on evaluation of memory cell proliferation after incubation with heavy metal salt [13,14]. This test is used in our study for diagnosis of metal intolerance.

Allelic components of the Major Histocompatibility Complex (MHC) are associated with various diseases and deviation of the immune response, including allergies to heavy metals [15]. Aten [1] demonstrated that the induction of autoimmunity by mercuric chloride is in rats related MHC Class II haplotype. Expression of MHC Class I molecules in Brown-Norway rats is modified by HgCl2 [10] and HgCl2 induced systemic autoimmunity is due to direct effect of this metal compound on activation potentials of T and B cells [9]. Jiang and Möller [6] analysed the unresponsiveness to HgCl2 of CD4 T cells in non-responder strains. Association of HLA-Class I and II with pe-
Table 1
Results of the Melisa™ test. SI are shown only for positive values. Negative values are given as *. For some the patients not all metals were tested (empty squares). The selection of metals to which sensitivity was tested was based on anamnestic information.

| Patient | Ag | Au | Cd | Co | Cr | Cu | Fe | Hg | Ni | Pb | Pd | Pt | Sn | Ti |
|---------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| 1       | *  | *  | *  | *  | *  | 3.55 | *  | *  | *  | *  | *  | *  | *  | |
| 2       | *  | *  | 2.26 | *  | *  | 11.8 | *  | *  | *  | *  | *  | *  | *  | |
| 3       | *  | 11.5 | 2.6 | 2.15 | 3.28 | 14.5 | 14.31 | *  | *  | *  | *  | *  | *  | |
| 4       | *  | 6.8 | 7.23 | 2.99 | 4.43 | 6.15 | 18.81 | 2.28 | *  | *  | 4.3 | 2.78 | |
| 5       | 2.34 | *  | *  | *  | *  | 3.07 | *  | *  | *  | *  | *  | *  | *  | |
| 6       | 3.25 | *  | *  | *  | *  | 29.95 | 3.57 | *  | *  | *  | *  | *  | *  | |
| 7       | *  | 4.01 | *  | *  | 2.67 | 14.45 | *  | *  | *  | *  | *  | *  | *  | |
| 8       | *  | 5.31 | *  | *  | *  | 3.08 | 3.88 | 3.58 | 3.32 | 2.06 | *  | *  | *  | |
| 9       | *  | *  | *  | *  | *  | *  | *  | *  | *  | *  | *  | *  | *  | |
| 10      | *  | *  | *  | *  | *  | *  | *  | *  | *  | *  | *  | *  | *  | |
| 11      | *  | *  | *  | *  | *  | *  | *  | *  | *  | *  | *  | *  | *  | |
| 12      | *  | *  | *  | *  | *  | *  | *  | *  | *  | *  | *  | *  | *  | |
| 13      | *  | *  | *  | *  | *  | 2.4 | *  | *  | *  | *  | *  | *  | *  | |
| 14      | *  | *  | *  | *  | *  | 2.08 | *  | *  | *  | *  | *  | *  | *  | |
| 15      | *  | *  | *  | *  | *  | 3.91 | 10.64 | *  | *  | *  | *  | *  | *  | |
| 16      | 2.72 | *  | 3.31 | 57.52 | *  | 2.11 | 7.05 | *  | *  | *  | *  | *  | *  | |
| 17      | *  | 12.33 | 8.5 | 2.92 | 17.18 | 2.47 | 3.61 | 2.65 | *  | *  | *  | *  | *  | |
| 18      | *  | *  | *  | *  | *  | *  | *  | *  | *  | *  | *  | *  | *  | |
| 19      | 2.84 | *  | *  | *  | *  | 3.91 | 10.64 | *  | *  | *  | *  | *  | *  | |
| 20      | *  | 4.28 | *  | *  | 3.24 | 16.45 | 2.61 | 9.44 | 4.88 | 5.49 | 17.88 | *  | *  | |
| 21      | 2.84 | *  | *  | *  | *  | 2.08 | *  | *  | *  | *  | *  | *  | *  | |
| 22      | 2.61 | *  | *  | *  | *  | 14.15 | 11.14 | *  | *  | *  | *  | *  | *  | |
| 23      | *  | *  | *  | *  | *  | *  | *  | *  | *  | *  | *  | *  | *  | |
| 24      | 4.04 | *  | *  | *  | *  | *  | *  | *  | *  | *  | *  | *  | *  | |
| 25      | *  | *  | *  | *  | *  | *  | *  | *  | *  | *  | *  | *  | *  | |

Riodontitis was recorded by Takashiba et al. [16] and Terasaki et al. [17].

Studies on HLA association with heavy metal intolerance or allergy are almost absent. Saito [11] described a significant increase of DR4 frequency (Relative risk = 13.27) in Japanese patients sensitive for palladium.

In our work we studied the HLA phenotypes in 25 patients with severe metal intolerance. These have been patients with serious allergic reactions examined at the Institute of Dental Research, Prague for consultation from the whole area of the Czech Republic.

2. Material and methods

Patients: Patients were identified as having local signs of intolerance to dental materials such as ptyalism, paraesthesia of the tongue and oral mucosa, ulcerations of the gingival tissue and oral mucous membrane and pigmentation following deposition of metals in the gum from amalgam fillings and other metal dental materials combined with general inconveniences as chronic fatigue, nausea, vomiting, head ache, increased perspiration, breathing discomfort. All these symptoms were related with dental interventions most frequently with dental fillings made by amalgam alloys and prosthetic reconstruction which included dental metal alloys. Allergy to metal was examined by the Melisa™ test [13] for the following metal compounds tested as allergens: Al₂O₃, CH₃COOAg, AuNa₃(S₂O₃)₂, CdCl₂, CoCl₂, CrCl₃, CuSO₄, Fe₂O₃, HgCl₂, phenylmercurycetate, methylmercuryc chloride, ethylmercuryc chloride, thiomersal, NiCl₂, Pb(NO₃)₂, PdCl₂, PtCl₄, SnCl₂ and TiO₂.

The stimulation index (SI) was calculated as the ratio of stimulated culture and average of values from non-stimulated cultures. According to values obtained from positive controls (samples stimulated with the polyclonal stimulator – Pokeweed mitogen – from Phyto-locica americana), the SI was evaluated as negative (SI < 2), positive (SI 2.0–3.0) and strong positive (SI > 3.0). The stimulation values (cpm) are expressed as count of ³H-thymidine incorporation per minute.

Typing of HLA antigens was performed by routine serological techniques (standard NIH microlymphocytoxicity test for Class I and prolonged incubation of B-lymphocytes isolated from PBL for Class II antigens) [5,17]. In total 47 HLA antigens were tested by sets of specific anti-HLA antisera.

Statistical evaluation was performed by the Fisher’s exact test. P < 0.05 are considered as significant.
The project was supported by grants 3472-3 and 3419-3, awarded by the Internal Grant Agency of the Ministry of Health of the Czech Republic.

References

[1] J. Aten, A. Veninga, E. deHeer, J. Rozing, P. Nieuwenhuis, P.J. Hoedemaeker and J.J. Weening, Susceptibility to the induction of either autoimmunity or immunosupression by mercury chloride is related to the MHC class II haplotype, *Eur. J. Immunol.* **21** (1991), 611–616.

[2] I. Bohm, M. Brody and R. Bauer, Comparison of personal history with patch test results in metal allergy, *J. Dermatol.* **24** (1997), 510–513.

[3] G.J. Bruce and W.B. Hall, Nickel hypersensitivity-related periodontitis, *Eur. Dent. Lett.* **16** (1995), 180–186.

[4] G. Ionescu, Allergotoxische Einflüsse von Umweltchadstoffen bei Allergiekranken, *Forsch. Komplementärmed.** 2** (1995), 2–8.

[5] E. Ivišková, Approvement of HLA antigens, in: *Chosen diagnostic methods in medical immunology* 1986, J. Procházková and C. John, eds, Avicenum, Prague, 1986, pp. 293–307.

[6] Y. Jiang and G. Möller, Unresponsiveness of CD4+ T cells from a non-responder strain to HgCl2 is not due to CD8+—mediated immunosupression: an analysis of the very early activation antigen CD69, *Scand. J. Immunol.* **44** (1996), 565–570.

[7] P. Panzner, Epicutanne tests, in: *Platform for clinical immunology* 1994, T. Fučková, J. Bartůňková, J. Litman and P. Panzner, eds, RDI’ PRESS and Agency KRIGL, Prague, 1994, pp. 112–113.

[8] L. Potolicchio, A. Festucci, P. Hausler and R. Sorrentino, HLA-DP molecules bind cobalt: a possible explanation for the genetic association with hard metal disease, *Eur. J. Immunol.* **29** (1999), 2140–2147.

[9] A. Roos, N. Claessen, J.J. Weening and J. Aten, Enhanced T lymphocyte expression of LFA-1, ICAM-1, and the TNF receptor family member OX40 in HgCl2-induced systemic autoimmunity, *Scand. J. Immunol.* **43** (1996), 507–518.

[10] A. Roos, E.I.M. Schilder-Tol, M.A. Chaud, J.J. Weening and J. Aten, HgCl2 and Il4 differentially modify expression of major histocompatibility complex class II molecules RT1.B and RT1.D in B lymphocytes from Brown Norway and Lewis rats, *Transplantation Proceedings* **29** (1997), 1675–1676.

[11] K. Saito, Analysis of genetic factor of metal allergy; polymorphism of HLA-DR, DQ genes, *Kokabyo Nogakai Zasshi* **63** (1996), 53–69.

[12] A.I. Selden, B. Persson, S.I. Bomerber-Denkvart, L.E. Windström and L.S. Bodin, Exposure to cobalt chromium dust
and lung disorders in dental technicians, *Thorax* **50** (1995), 769–772.

[13] V.D.M. Stejskal, K. Cederbrandt, A. Lindvall and M. Forsbeck, MELISA – an in vitro tool for the study of metal allergy, *Toxicol. in vitro* **5** (1994), 991–1000.

[14] V.D.M. Stejskal, M. Forsbeck, K. Cederbrandt and O. Åsteman, Mercury-specific lymphocytes: an indication of mercury allergy in man, *J. Clin. Immunol.* **16** (1996), 31–40.

[15] N. Suzuki, Metal allergy in dentistry: detection of allergen metals with X-ray fluorescence spectroscope and its application toward allergen elimination, *Int. J. Prosthodent.* **8** (1995), 351–359.

[16] S. Takashiba, S. Noji, F. Nishimura, H. Ohyama, H. Kurihara, Y. Namura, S. Tanigushi and Y. Murayama, Unique intronic variations of HLA-DQβ gene in early onset periodontitis, *J. Periodontol.* **65** (1994), 379–386.

[17] P.I. Terasaki, R.S. Kaslick, T.L. West and A.I. Chasens, Low HLA-A2 frequency and periodontitis, *Tissue Antigens* **5** (1975), 286–288.