

Serum and parotid salivary IgA in chronic bronchitis and asthma

D. I. M. SIEGLER and K. M. CITRON

Cardiothoracic Institute, Brompton Hospital, London

Siegler, D. I. M. and Citron, K. M. (1974). *Thorax*, 29, 313–316. **Serum and parotid salivary IgA in chronic bronchitis and asthma.** It has been suggested that immunoglobulin A (IgA) deficiency may be an important predisposing factor to infection in chronic bronchitis and that this occurs more often in extrinsic asthmatics than in normal subjects. These claims have been investigated by measurement of IgA in stimulated parotid saliva and serum in chronic bronchitics and asthmatics. Salivary and serum IgA levels in 84 chronic bronchitics could not be correlated with sputum purulence, the degree of ventilatory impairment, radiographic evidence of emphysema or the smoking history. Serum IgA was low in 6% and salivary IgA was normal in all cases. IgA levels measured in both serum and saliva in 50 asthmatics showed no correlation with the number of positive skin tests or other evidence of atopy. Serum IgA was low in 8% and salivary IgA was normal in all cases.

The bronchopulmonary tree possesses a variety of defence mechanisms against infection. These mechanisms may be divided into two main groups. Firstly, there are the non-specific defences including mucociliary transport, phagocytosis by polymorphs and other cells, and the secretion of humoral substances such as lysozyme, lactoferrin, properdin, and interferon. Secondly, there are locally produced antibodies comprising the secretory immunoglobulins. Interest in these locally secreted immunoglobulins has increased rapidly since the early 1960s when IgA was demonstrated to be the principal immunoglobulin in exocrine secretions (Chodirker and Tomasi, 1963; Tomasi and Bienenstock, 1968). IgA in the respiratory tract may arise both from local production and from the serum and plays an important part in the defences of the respiratory tract against a variety of infections, both viral and bacterial.

It has been suggested (Medici and Buergi, 1971) that the liability to respiratory infection in chronic bronchitis may be associated with quantitative or possibly qualitative abnormality of local secretory IgA.

Interest has also been focused on the role of IgA in atopic asthma. Kaufman and Hobbs (1970) demonstrated serum IgA deficiency to be more frequent in one group of atopic subjects than in normals.

The purpose of the present study was to ascertain whether serum or salivary IgA deficiency could be implicated in the recurrent infections of chronic bronchitis and whether IgA deficiency could be identified in a group of adult asthmatics.

Bronchial secretion is the medium most relevant to studies of local IgA in the respiratory tract. However, its collection would involve bronchoscopy, thus raising ethical objections. The interpretation of the IgA content of expectorated sputum is open to a wide variety of errors since such sputum is a mixture of bronchial secretions, saliva, and possibly tissue fluid transudates. As an alternative, parotid saliva was chosen for this study because of its ease of collection and freedom from contamination. It must be accepted that changes in IgA in saliva may not mirror levels in bronchial secretions or in other parts of the respiratory tract.

METHODS

Parotid saliva, stimulated by the introduction of 5 ml of 10% citric acid into the mouth, was collected by means of a Curby (1953) cup. A blood sample was taken from each patient at the same time. IgA was measured in the serum by radial immunodiffusion on plates supplied by Hoechst and in saliva on low IgA reading (1–10 mg per 100 ml) plates supplied by the same manufacturer. IgA in saliva was measured

against a 7S standard. This method measures total IgA, that is both secretory IgA and free IgA.

RESULTS

CHRONIC BRONCHITIS Eighty-four patients with chronic bronchitis conforming to the Medical Research Council definition (Medical Research Council, 1965) were studied. There were 68 males and 16 females, their ages ranging between 47 and 84 years. All salivary IgA levels were within the normal range of Oon and Lee (1972) of 0.7 to 9.3 mg/100 ml with a mean value of 2.6 mg/100 ml against a mean normal of 2.3 mg/100 ml: this difference is not significant. Mean serum IgA for the group was 338 mg/100 ml (mean normal 300 ± 150 mg/100 ml). The serum levels were below the lower limits of normal (125 mg/100 ml) in five patients (6%). These levels were 114, 110, 103, 80, and 62 mg/100 ml. The last two patients had mucoid sputum and the others purulent sputum. No correlation was found between the levels of IgA in serum and saliva.

The patients were divided into those with predominantly mucoid sputum throughout the year and those with predominantly purulent sputum. Predominantly purulent sputum was defined as the presence of purulent or mucopurulent sputum throughout most of the year. Sputum purulence was assessed by observing a sputum specimen provided on each of three separate clinic visits. The patient's opinion of the usual state of his sputum was also obtained.

Figures 1 and 2 show the correlation between salivary IgA and serum IgA respectively and degree of sputum purulence. The differences were

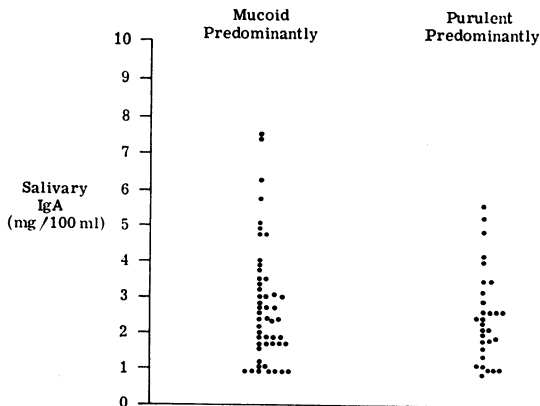


FIG. 1. Salivary IgA levels in chronic bronchitics whose sputum was predominantly mucoid or predominantly purulent.

not statistically significant. In the great majority of patients the state of the sputum at the time of collection of the saliva and blood specimens was the usual sputum state during the year. No statistical correlation could be obtained between serum and salivary IgA and, in addition, serum and salivary IgA could not be correlated with:

- (a) degree of ventilatory impairment as measured by the forced expired volume in one second expressed as a percentage of predicted value;
- (b) presence or absence of emphysema on the chest radiograph;
- (c) smoking history.

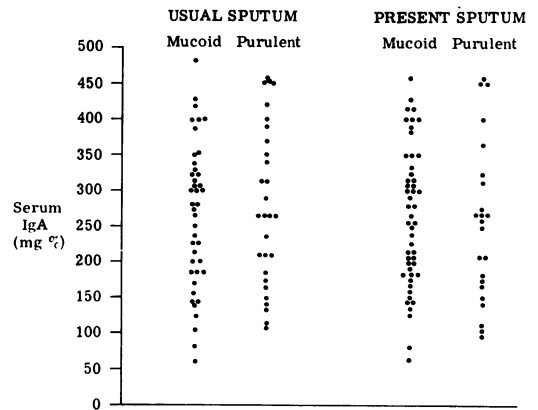


FIG. 2. Serum IgA levels in chronic bronchitics. The patients are divided according to whether their sputum was usually mucoid or purulent and also according to the state of the sputum when the sample of serum was taken.

The possibility that salivary IgA may vary widely from time to time in the individual patient was also investigated. Three patients were studied monthly for four months, samples being collected at the same time of the same day each time; the variation in salivary IgA was small in each, viz., 1.0 to 1.2 mg/100 ml, 1.2 to 1.7 mg/100 ml, and 1.0 to 2.0 mg/100 ml.

ASTHMA Fifty asthmatic patients were studied, 17 male and 33 female, the age range 15 to 74 years. All salivary IgA levels were within normal limits. Mean salivary IgA for the group was 2.1 mg/100 ml and mean serum IgA 221 mg/100 ml: these did not differ significantly from the mean normal values given above. Serum levels were below the lower limit of normal (125 mg/100 ml) in four patients (8%). These levels were 110, 110, 103, and 58 mg/100 ml. Salivary levels of IgA did not correlate with serum levels.

In Fig. 3, the salivary IgA levels are shown for extrinsic and intrinsic asthmatic subjects. The mean salivary IgA of 16 intrinsic asthmatics with no positive skin tests was 2.6 mg/100 ml and that of 28 extrinsic asthmatics with three or more positive skin tests was 2.0 mg/100 ml: the difference was not significant. Serum IgA did not correlate with the number of positive skin tests.

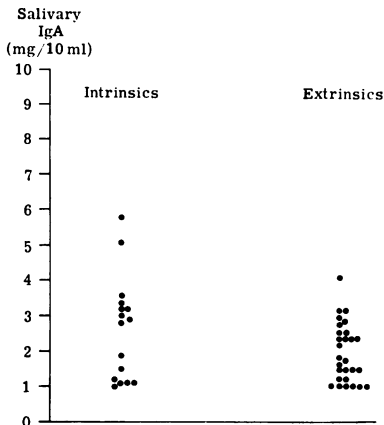


FIG. 3. Salivary IgA levels in intrinsic and extrinsic asthmatics.

In addition, an attempt was made to correlate serum and salivary IgA with the additional presence of allergic rhinitis and/or eczema. No correlation was obtained. As in the bronchitic group there was no correlation between serum and salivary IgA.

DISCUSSION

Parotid and serum IgA in this group of bronchitics showed no correlation with a variety of clinical features of the disease. In particular, there was no evidence that a low parotid or serum IgA could be correlated with a higher incidence of bronchial infection suggested by the persistence of purulent sputum.

A normal parotid IgA cannot be taken to imply that the level of IgA in bronchial secretions is likewise normal. For the reasons stated above, no attempt was made to estimate IgA in expectorated sputum. However, Falk, Okinaka, and Siskind (1972) obtained bronchial secretion at bronchoscopy in six chronic bronchitics and found IgA levels which they regarded as normal. Alford (1968) measured nasal secretory IgA in 24 patients with chronic bronchitis and emphysema and found no differences from the controls.

Sputum IgA was estimated by Medici and Buerger (1971) in chronic bronchitics. These authors found higher levels in patients with mild or moderate symptoms compared with patients with far-advanced disease. In view of their findings of absent 'secretory piece' in some patients with far-advanced disease, they postulated a disturbance of production of 'secretory piece' as a result of damage to bronchial epithelium.

Differences in quantities of IgA detectable in secretions may bear little relationship to the specific antibacterial or antiviral activities of IgA. Hence, the findings in this study do not exclude the possibility that chronic bronchitics who are habitually infected may lack specific antibacterial IgA or, alternatively, the possibility of some qualitative difference in the IgA molecule such as disruption of the 'secretory piece' which is thought to protect 'secretory IgA' from proteolytic digestion.

Moreover the parotid gland may not be exposed to the antigenic bombardment occurring in the respiratory tract. Thus, Waldman, Small, and Rowe (1969) have shown that local immunization to influenza virus antigens by inhalation may result in specific antibodies being produced in nasal and bronchial secretions, but to a much lesser extent in parotid saliva.

Our estimations of salivary IgA reported at monthly intervals showed remarkably constant levels in individual patients. Notable variations in salivary IgA levels estimated by a different technique were reported by Lewis, Lapp, and Burrell (1970). The difference may well be due to the method used for salivary stimulation. The technique used by us for obtaining stimulated parotid saliva gives a relatively narrow range of values.

Salivary IgA levels did not correlate with smoking history in our bronchitics: this is in agreement with previous work (Lewis *et al.*, 1970) in which salivary IgA was reduced in cigarette smokers without bronchitis but was normal in cigarette-smoking bronchitics.

The decline in nasal secretory IgA with age described by Alford (1968) was not confirmed in parotid salivary IgA in the present study.

Kaufman and Hobbs (1970) analysed 641 patients with a wide variety of atopic diseases, of whom 30 had serum IgA deficiency, the prevalence of which was some 35 times higher than expected. We found no case of severe serum IgA deficiency. The incidence of low serum IgA levels in our adult asthmatics (8%) was not greatly different from that in our bronchitics (6%). We

found no evidence that serum or salivary IgA deficiency occurred unduly frequently in adult asthmatics. This does not conflict with the recent evidence that delay in the development of normal levels of serum IgA in infancy may predispose to atopic disease (Taylor *et al.*, 1973) or that atopic disease other than asthma in adults may be associated with increased frequency of IgA deficiency.

Our studies of serum and parotid IgA in only 50 patients showed no evidence of correlation between the degree of atopy and these measurements. Hobday, Cake, and Turner (1971) showed no difference of nasal secretion IgA levels between asthmatic children and controls, and Salvaggio *et al.* (1973b) found no differences in IgA content of saliva, nasal wash fluids, and sputum between atopics and controls. However, Salvaggio *et al.* (1973a) found lower nasal wash titres to intranasally administered tetanus, thus providing evidence that whereas there appears to be no quantitative difference in secretory IgA levels between adult atopics and normals, qualitative differences can be detected. Further research into specific IgA antibodies should throw further light on this problem.

We wish to thank Professor M. Turner-Warwick and Professor J. R. Hobbs for much helpful discussion and practical criticism. We also acknowledge the technical help of Mrs. Judith Weekes.

REFERENCES

- Alford, R. H. (1968). Effects of chronic bronchopulmonary disease and aging on human nasal secretion IgA concentrations. *Journal of Immunology*, **101**, 984.
- Chodirker, W. B. and Tomasi, T. B. (1963). Gamma-globulins: quantitative relationships in human serum and non-vascular fluids. *Science*, **142**, 1080.
- Curby, W. A. (1953). Device for collection of human parotid saliva. *Journal of Laboratory and Clinical Medicine*, **41**, 493.
- Falk, G. A., Okinaka, A. J., and Siskind, G. W. (1972). Immunoglobulins in the bronchial washings of patients with chronic obstructive pulmonary disease. *American Review of Respiratory Disease*, **105**, 14.
- Hobday, J. D., Cake, M., and Turner, K. J. (1971). A comparison of the immunoglobulins IgA, IgG, IgE in nasal secretions from normal and asthmatic children. *Clinical and Experimental Immunology*, **9**, 577.
- Kaufman, H. S. and Hobbs, J. R. (1970). Immunoglobulin deficiencies in an atopic population. *Lancet*, **2**, 1061.
- Lewis, D. M., Lapp, N. L., and Burrell, R. (1970). Quantitation of secretory immunoglobulin A in chronic pulmonary disease. *American Review of Respiratory Disease*, **101**, 55.
- Medical Research Council (1965). Definition and classification of chronic bronchitis for clinical and epidemiological purposes. *Lancet*, **1**, 775.
- Medici, T. C. and Buergi, H. (1971). The role of immunoglobulin A in endogenous bronchial defence mechanisms in chronic bronchitis. *American Review of Respiratory Disease*, **103**, 784.
- Oon, C. H. and Lee, J. (1972). A controlled quantitative study of parotid salivary secretory IgA globulin in normal adults. *Journal of Immunological Methods*, **2**, 45.
- Salvaggio, J. E., Lopez, M., Arquembourg, P., Waldman, R. H., and Sly, M. (1973a). Salivary nasal wash, and sputum IgA concentrations in atopic and non-atopic individuals. *Journal of Allergy and Clinical Immunology*, **51**, 335.
- , Waldman, R. H., Fruchtman, M. H., Wigley, F. M., and Johnson, J. E. (1973b). Systemic and secretory antibody response of atopic and non-atopic individuals to intranasally administered tetanus toxoid. *Clinical Allergy*, **3**, 43.
- Taylor, B., Norman, A. P., Orgel, H. A., Stokes, C. R., Turner, M. W., and Soothill, J. F. (1973). Transient IgA deficiency and pathogenesis of infantile atopy. *Lancet*, **2**, 111.
- Tomasi, T. B. and Bienenstock, J. (1968). Secretory immunoglobulins. *Advances in Immunology*, **9**, 1.
- Waldman, R. H., Small, P. A., and Rowe, D. S. (1969). *The Secretory Immunologic System*, p. 130.

Requests for reprints to: Dr. K. M. Citron, Cardiothoracic Institute, Brompton Hospital, London SW3.