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# Dupuytren's contracture, chronic liver disease and IgA immune complexes

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ABSTRACT – Contrary to previous reports, Dupuytren's contracture was found to be equally common in patients with alcoholic and non-alcoholic biopsy-proven liver disease (25% v 28%). Furthermore, in 69 patients with Dupuytren's contracture referred for surgical correction, there was no significant increase in either history of alcohol abuse or abnormality of liver function compared to a matched control group. Patients with Dupuytren's contracture were found to have increased levels of circulating IgA immune complexes compared to those without ($p<0.05$ for those with liver disease; $p<0.001$ for those awaiting surgical correction). Circulating immunoglobulins and immune complexes of other classes were similar between the groups with and without Dupuytren's contracture. These results suggest that the importance of alcohol has previously been exaggerated but that IgA immune complexes may be involved in the pathogenesis of the condition.

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Dupuytren's disease, recognised by a painless flexion contracture of the hand, has been associated with a number of conditions including alcoholic liver disease, epilepsy and diabetes. The pathogenesis of the condition is unknown, but it has recently been suggested that immune mechanisms may be important in the development of the disease (1, 2).

The association with liver disease is well recognised and Wolff et al. (3) demonstrated Dupuytren's contracture (DC) to be present in 47% of patients with alcoholic liver disease but in only 11.1% of patients with other forms of chronic liver disease. Similar findings for these patient groups were obtained by Nazari (4) who reported an incidence of 54.8% and 3.5%, respectively. Su & Patek (5) suggested that this association was related to alcohol excess and not to the presence of chronic liver disease, as a similar incidence was found in alcoholics with and without established liver disease (18% and 19.2%, respectively). Some support for this theory emerges from another study in which 25% of all alcoholics had evidence of DC (6).

As a result of these findings, it has been accepted that in patients with chronic liver disease DC is primarily a feature of alcoholic liver disease. However, review of these studies shows that many of the patients had not undergone liver biopsy and patients with con-

ditions such as metastatic tumour or obstructive jaundice were included in the non-alcoholic liver disease group. The aim of this study was therefore to investigate the incidence of DC in patients with biopsy-proven cirrhosis. To gain insight into the importance of alcohol in the development of the disease, patients with DC attending an orthopaedic clinic for surgical correction were investigated for alcohol abuse and the presence of liver disease.

As circulating IgA levels are sometimes increased in alcoholic liver disease compared to other forms of liver disease (7), and because increased IgG and IgA levels have been reported in patients with DC (2), we also measured immunoglobulin and circulating immune complex levels in these patients.

## Patients and methods

Sixty-eight patients with biopsy-proven chronic liver disease attending an out-patient clinic were examined for evidence of DC. Three grades of severity of DC were recognised. Grade 1 consisted of palmar nodules with skin puckering, grade 2 indicated flexion of the fingers of less than 45° and grade 3 flexion of more than 45°. All these patients were classified on liver biopsy as having alcoholic or non-alcoholic liver disease.

A further group of 69 patients attending an out-patient hand clinic and awaiting surgical correction of their DC was studied. These patients were questioned regarding their alcohol intake, examined for the presence of liver disease and blood was taken for a full blood count, standard liver function tests, including gamma glutamyl transferase, and serum collected for measurement of circulating immunoglobulins and immune complexes. Fifty-seven patients attending a surgical day unit for minor operations were used as a control group and were of similar age and sex distribution.

Serum for the immunoglobulin estimation was snap-frozen and stored at −70° until assay. That for immune complexes was stored at 4°C and assayed within 7 days. Serum levels of IgG, IgA, IgM, C3c and CIq were measured using single radial immunodiffusion (Mercia Brocades Ltd., Weybridge, Surrey). Circulating immune complexes were measured using the Merrid CIC profiling kit (Mercia Brocades Ltd.). Briefly, immune complexes were precipitated from sera by 2% polyethylene glycol (PEG) and analysed for immunoglobulin (IgG, IgA and IgM) and complement (C3c and CIq) components by single radial-immunodiffusion. Student's *t*-test was used for analysis and a probability of 5% for type 1 error was considered to be significant.

## Results

Nineteen of the 69 patients with known chronic liver disease (27.9%) were found to have DC.

Table 1
Details of patients with chronic liver disease divided into those with and without Dupuytren's contracture (DC)

| | Patients with DC | Patients without DC |
|---|---|---|
| Total | 19 | 49 |
| Age (mean±1 S.D.) | 64.1±8.0 | 57.1±13.2 |
| Sex | M 10 F 9 | M 31 F 18 |
| Diagnosis: | | |
| Alcoholic liver disease | 8 (42.1%) | 24 (48.9%) |
| Haemachromatosis | 1 | 2 |
| Chronic active hepatitis | 5 | 7 |
| Primary biliary cirrhosis | 2 | 8 |
| Cryptogenic cirrhosis | 1 | 4 |
| Drug-induced chronic hepatitis | 1 | – |
| Hereditary telangiectasia | – | 1 |
| Sclerosing cholangitis | – | 1 |
| $\alpha_1$-antitrypsin deficiency | 1 | 2 |

Table 2

Findings in patients with Dupuytren's contracture (DC) attending an orthopaedic clinic (N=69) compared to controls (N=57)

| | Patients with DC | Controls |
|---|---|---|
| Age | 62.2±10.4 | 62±11.3 |
| Sex | M 57<br>F 12 | M 50<br>F 7 |
| History suggesting excessive alcohol intake ( >80 g daily) | 6 (8.6%) | 2 (3.6%) |
| Physical signs: | | |
| Hepatomegaly | 3 | 1 |
| Splenomegaly | 1 | 0 |
| Palmar erythema | 4 | 1 |
| Investigations: | | |
| Total with any biochemical abnormality | 7 (10.1%) | 4 (7.2%) |
| Elevated γGT | 7 | 4 |
| Elevated transaminase | 1 | 0 |
| Elevated alkaline phosphate | 1 | 0 |
| Increased mean cap. vol. | 3 | 2 |

The diagnosis and other details of these patients with and without Dupuytren's contracture are shown in Table 1. Thirty-two of these 69 patients were classified as having alcoholic liver disease, and of these, eight (25%) had DC (four grade 1, three grade 2, one grade 3). DC was slightly more common in the non-alcoholic groups and was found in 11 (30.5%) of the 36 patients (eight grade 1, three grade 2). Of the total of 19 patients with DC, only four had bilateral disease and only one had a family history of the condition.

The findings in the patients with DC attending the orthopaedic clinic and in the control group are shown in Table 2. There were nine with grade 1 contracture, 29 with grade 2 and 31 with grade 3. Forty-seven (68%) were found to have bilateral disease and 17 (25%) had a positive family history of DC. Although slightly more patients in the DC group admitted to a high alcohol intake (8.6% compared to 3.6%), an approximately similar number in each group showed biochemical evidence suggesting liver disease (10.1% v 7%). However, all abnormalities were mild.

Results of the immunoglobulin and immune

Table 3

Values of circulating immunoglobulins and immune complexes in patients with biopsy-proven liver disease with (N=14) and without (N=34) Dupuytren's contracture (DC). Results shown as mean±SD

| | IgG | IgM | IgA | C3 | Clq |
|---|---|---|---|---|---|
| Immunoglobulin (mg/ml) | | | | | |
| With DC | 13.91±6.13 | 2.97±1.43 | 4.34±2.45 | - | - |
| Without DC | 13.60±6.14 | 2.13±1.31 | 3.46±2.41 | - | - |
| Immune complexes (μg/ml) | | | | | |
| With DC | 217.7±78.6 | 104.8±57.8 | 52.8±24.7* | 32.8±20.8 | 90.1±38.3 |
| Without DC | 167.7±83.7 | 94.6±67.5 | 34.8±26.4 | 22.6±16.4 | 92.4±53.0 |

*=$p<0.05$.

Table 4

Values of circulating immunoglobulins and immune complexes in patients with Dupuytren's contracture (DC) attending an orthopaedic clinic (N=69) and controls (N=54). Results shown as mean±SD

| | IgG | IgM | IgA | C3 | Clq |
|---|---|---|---|---|---|
| Immunoglobulin (mg/ml) | | | | | |
| DC | 10.07±3.06 | 2.23±2.98 | 2.13±1.11 | 1.38±0.41 | .1915±.0028 |
| Controls | 9.54±3.30 | 1.71±1.06 | 1.83±0.96 | 1.24±0.42 | .1912±.0319 |
| Immune complexes (μg/ml) | | | | | |
| DC | 101.7±44.4 | 64.6±37.6 | 21.1±9.9** | 30.1±16.0 | 68.3±26.3 |
| Controls | 87.9±62.0 | 51.6±38.4 | 13.3±7.59 | 25.6±18.3 | 70.3±38.3 |

**=$p<0.001$.

complex assays in the patients with liver disease and in those attending the orthopaedic clinic are shown in Tables 3 and 4. As expected, levels of immunoglobulin and immune complexes were generally raised in those patients with liver disease (7, 8). The only difference between patients with or without DC was a highly significant increase in circulating IgA immune complexes in those with DC ($p<0.05$ for patients with liver disease, $p<0.001$ for those without). The individual values for IgA immune complexes in patients awaiting surgical correction are shown in Fig. 1. Since small amounts of serum IgA are precipitated by 2% PEG, apparently raised levels of complexed IgA could be caused by a high concentration of serum IgA. Although IgA levels were not elevated in patients with DC, to further exclude this possibility we calculated the amount of IgA precipitated by PEG as a percentage of the total serum IgA for each patient. The mean of this value was 1.22±0.87% for the patients with DC awaiting surgical correction and 0.82±4.6% for the control group ($p<0.005$). There was no significant difference between those patients with liver disease with or without DC (1.42±0.65%, 1.07±0.46%).

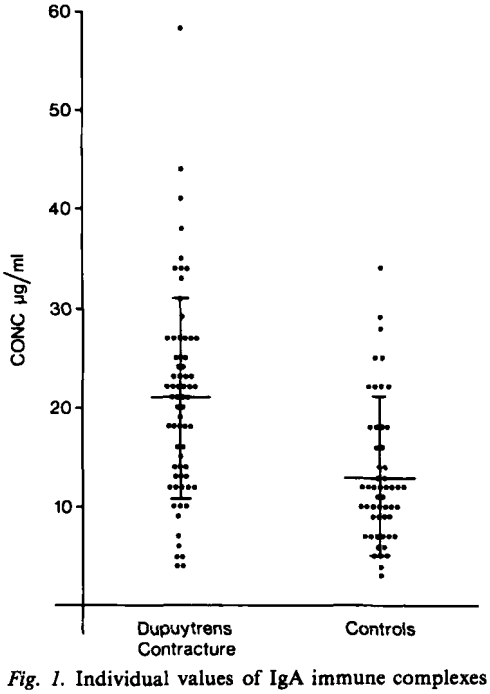


*Fig. 1.* Individual values of IgA immune complexes in patients with Dupuytren's contracture attending an orthopaedic clinic and in controls.

## Discussion

These results demonstrate that DC may be associated with all forms of chronic liver disease and is no more common in patients with alcoholic than non-alcoholic liver disease. The incidence found in alcoholic liver disease in this study is similar to that found in previous studies. The incidence found in those with other forms of liver disease is higher than in previous studies and is probably explained on the basis of

all our patients having biopsy-proven disease. Most patients with liver disease had early stage DC and only two complained of disability due to this disease. This observation, together with the absence of either bilateral disease or a family history, all features in sharp contrast to those patients attending the orthopaedic clinic, suggests that the pathogenesis of the contracture in patients with chronic liver disease may be different from that in the normal population.

Reviewing patients with established DC has failed to show a significant increase in either evidence of alcohol abuse or in abnormal liver function compared to a group of controls. Although numbers are relatively small, this does suggest that alcohol and coexistent liver disease are relatively unimportant in the development of the condition. Certainly the presence of DC should not be considered to be suggestive of either alcohol excess or coexistent liver disease.

We have been unable to confirm the previously reported abnormalities of IgA and IgG levels in patients with DC (2). However, the finding of elevated levels of circulating IgA immune complexes in patients with DC is of interest as it provides further evidence of an abnormal immune mechanism in patients with DC. The generalized increase in circulating immune complexes of all classes in the patient with liver disease probably explains the less clear-cut results obtained between those with and without DC in this group. Finally, we do not know whether the specific increase in IgA immune complexes in DC represents a primary, and hence pathogenetically important, or a secondary phenomenon.

In conclusion, this study confirms that DC is common in all forms of chronic liver disease but suggests that previous studies have overemphasised the importance of alcohol in its development. The finding of an excess of IgA immune complexes in patients with Dupuytren's contracture is not readily explained but may suggest that immune mechanisms are involved in the pathogenesis of the condition.

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