Linear IgA Bullous Dermatosis
A Retrospective Study of 23 Patients in Denmark
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Linear IgA bullous dermatosis (LAD) is an autoimmune, chronic bullous disease affecting primarily young children and adults. Studies on LAD are relatively sparse and from Scandinavia we could only find a few case reports. Therefore we decided to conduct a retrospective investigation of patients seen at our department since 1972. A total of 23 patients were identified; 7 children (F:M ratio 0.75) and 16 adults (F:M ratio 0.78). Mean age at disease onset in the two age groups were 2.7 and 56.8 years. Estimated incidence rate in our region: 0.67 per million per year. The most commonly used treatment modalities were corticosteroids, dapsone and sulphaspyridine. Key words: IgA; bullous disease; autoimmune disease; chronic bullous disease of childhood; treatment; incidence; Naranjo algorithm.

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Linear IgA bullous dermatosis (LAD) is an autoimmune, chronic bullous disease affecting primarily young children and adults. Childhood onset LAD is also named chronic bullous disease of childhood (CBDC) and is characterised by the development of papulovesicles and larger bulla primarily around the mouth and eyes, lower abdomen, thighs, buttocks, genitals, wrists and ankles (Fig. 1 and Fig. 2). The lesions can be annular or polycyclic urticarial plaques with a characteristic blistering along the edge of the lesion, the so-called “string-of-pearls” sign (Fig. 1B). Involvement of the mucosa can be seen. The subjective symptoms are variable from almost none or mild pruritus to severe burning.

The adult-onset form of LAD has a slightly different presentation with lesions on the trunk (Fig. 1D) and sometimes head and limbs. The blisters arise on urticarial looking plaques or normal skin. Mucosa can be affected. The string-of-pearls sign is less common in adults compared with the childhood form (1).

Histological characteristic features include a subepithelial blister formation with neutrophils along the basement membrane zone (BMZ). Direct immunofluorescence typically shows a linear IgA deposition along the BMZ, in some cases both IgA and IgG while rarely IgM and C3 can be seen (2).

Studies on LAD are relatively sparse and most of the publications are small series or single case reports. From Scandinavia we could only find a few case reports (3–6). Therefore, we decided to conduct a retrospective investigation of patients seen at our department since 1972. The objective is to give a description of the different subgroups of patients with LAD with regard to

Fig. 1. Linear IgA bullous dermatosis. (A) Numerous tense bullae on neck and face including periorbital and perioral area (patient No. 5). (B) “String-of-pearls” sign (patient No. 5). (C) Polycyclic bullae on urticarial looking plaques characteristically localised in the genital region (patient No. 6). (D) Maculopapular lesions symmetrically distributed on the back (patient No. 9).
precipitating factors, demographics, treatments, course of disease, and differential diagnoses.

Furthermore, our study is the first study to give an estimated incidence rate of the disease in our region.

METHODS

After approval from the records of patients with LAD seen at the Department of Dermatology, Odense University Hospital, Denmark from the beginning of January 1972 until January 2014 were reviewed. Inclusion criteria from 1972–1994 were the ICD8-diagnosis 693.09 Linear IgA dermatosis. From January 1994 until January 2014 inclusion criteria were the ICD-10 diagnoses L 13.8 Other specified bullous disorders, and L12.2 Chronic bullous disease of childhood.

Patient data regarding age at disease onset, gender, medical associations, medications, immunofluorescence findings, other investigations, disease duration, treatment, and tentative diagnosis were recorded.

RESULTS

A total of 23 patients were identified; 7 children and 16 adults.

Children

The child group (Table I) included 4 boys and 3 girls (F:M ratio 0.75). Their mean age at disease onset in childhood was 2.7 years (range 11 months–4 years, median 3 years).

The most common initial tentative clinical diagnoses were bullous impetigo \((n=3)\), erythema multiforme \((n=2)\), herpes simplex \((n=1)\) and chickenpox \((n=1)\).

Direct immunofluorescence was performed in all cases and showed linear IgA deposition. One had a combined linear IgA/IgG deposition. Indirect immunofluorescence investigation was performed in 3 cases and 2 of these were positive. None of the children had a history of drug intake.

Four of the children were primarily treated with dapsone, and 3 of these later switched to treatment with sulphaspyridine. Three of the children were primarily treated with sulphaspyridine but later changed to treatment with dapsone. Three patients received concomitant systemic prednisone with a dosage of 0.5–1 mg/kg/day. Typical dapsone dosage was 0.5–2 mg/kg/day and sulphaspyridine dosage was 100–200 mg/kg/day.

The reasons for changing treatment modalities were poor response or side effects (fever, rash, malaise). The mean duration of treatment was 3.2 years (range 2–6 years, median 3 years).

Adults

Among 16 adults with LAD (Table II) there were 7 women and 9 men (F:M ratio: 0.78). The mean age at time of disease onset was 56.8 years (range 23–79 years, median 63.5 years).

The tentative clinical diagnoses in the adult group were bullous pemphigoid \((n=4)\), dermatitis herpetiformis \((n=2)\), Stevens-Johnsons syndrome \((n=2)\), eczema \((n=2)\), bullous dermatitis not specified \((n=2)\), bullous multiforme \((n=1)\), bullous impetigo \((n=1)\) acquired epidermolysis bullosa \((n=1)\) and dermatophytosis \((n=1)\).

Table I. Seven children with linear IgA dermatosis, all with complete response

<table>
<thead>
<tr>
<th>Pat. No.</th>
<th>Age, years/sex</th>
<th>Direct IF</th>
<th>Indirect IF</th>
<th>HLA-B8</th>
<th>Treatment</th>
<th>Duration of treatment</th>
<th>Tentative diagnosis at presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3/M</td>
<td>Linear IgA</td>
<td>+</td>
<td>+</td>
<td>Sulphapyridine, Dapsone, Prednisolone</td>
<td>6 years</td>
<td>Bullous impetigo</td>
</tr>
<tr>
<td>2</td>
<td>2/M</td>
<td>Linear IgA</td>
<td>–</td>
<td>+</td>
<td>Dapsone, Prednisolone, Sulphapyridine</td>
<td>2 years</td>
<td>Bullous erythema multiforme</td>
</tr>
<tr>
<td>3</td>
<td>0.9/F</td>
<td>Linear IgA</td>
<td>ND</td>
<td>ND</td>
<td>Dapsone, Sulphapyridine</td>
<td>3 years</td>
<td>Herpes or erythema multiforme</td>
</tr>
<tr>
<td>4</td>
<td>3/M</td>
<td>Linear IgA</td>
<td>ND</td>
<td>+</td>
<td>Topical steroid, Dapsone</td>
<td>3 years</td>
<td>Varicella</td>
</tr>
<tr>
<td>5</td>
<td>4/F</td>
<td>Linear IgA</td>
<td>+</td>
<td>+</td>
<td>Dapsone, Prednisolone, Sulphapyridine</td>
<td>1.5 years</td>
<td>Bacterial infection</td>
</tr>
<tr>
<td>6</td>
<td>2/M</td>
<td>Combined linear IgA/IgG</td>
<td>ND</td>
<td>ND</td>
<td>Sulphapyridine, Prednisolone, Dapsone</td>
<td>3 years</td>
<td>Bullous impetigo</td>
</tr>
<tr>
<td>7</td>
<td>3/F</td>
<td>Linear IgA</td>
<td>ND</td>
<td>ND</td>
<td>Sulphapyridine, Dapsone</td>
<td>4 years</td>
<td>Bullous impetigo</td>
</tr>
</tbody>
</table>

IF: immunofluorescence; ND: Not done; +: positive; –: negative.
### Table II. Sixteen adults with linear IgA dermatosis

<table>
<thead>
<tr>
<th>Pat. No.</th>
<th>Age, sex</th>
<th>Previous disease</th>
<th>Culprit drug(s)</th>
<th>Direct IF</th>
<th>Indirect IF</th>
<th>HLA-B8</th>
<th>Treatment</th>
<th>Duration of treatment</th>
<th>Response</th>
<th>NS</th>
<th>Tentative diagnosis at presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>76/M</td>
<td>Bladder cancer, arthritis temporalis</td>
<td>Isoniazid</td>
<td>Linear IgA</td>
<td>ND</td>
<td>ND</td>
<td>Drug withdrawal, topical steroid, prednisone</td>
<td>2 years</td>
<td>CR</td>
<td>3</td>
<td>Bullous pemphigoid</td>
</tr>
<tr>
<td>9</td>
<td>79/M</td>
<td>Diabetes, diarrhoea</td>
<td>Metronidazole, Loperamide, Metoclopramide, Pivampicillin, Digoxin, Loperamide</td>
<td>Linear IgA, IgG</td>
<td>ND</td>
<td>ND</td>
<td>Drug withdrawal, prednisone</td>
<td>3 months</td>
<td>CR</td>
<td>4</td>
<td>Stevens-Johnson syndrome (Erythema multiforme)</td>
</tr>
<tr>
<td>10</td>
<td>68/M</td>
<td>Heart surgery</td>
<td>Penicillin, Diethylcarbamazine</td>
<td>Linear IgA</td>
<td>ND</td>
<td>ND</td>
<td>Drug withdrawal, prednisone</td>
<td>1 month</td>
<td>CR</td>
<td>4</td>
<td>Stevens-Johnson syndrome</td>
</tr>
<tr>
<td>11</td>
<td>62/M</td>
<td>Allergic alveolitis</td>
<td>Penicillin, Diethylcarbamazine, Dimethoxyphenylpenicillin, Cefuroxime, Fluconazole</td>
<td>Linear IgA</td>
<td>-</td>
<td>ND</td>
<td>Drug withdrawal, topical steroid, prednisone</td>
<td>2 months</td>
<td>CR</td>
<td>5</td>
<td>Unknown</td>
</tr>
<tr>
<td>12</td>
<td>65/F</td>
<td>Pneumonia, alcoholism</td>
<td>Penicillin, Diethylcarbamazine, Dimethoxyphenylpenicillin, Cefuroxime, Fluconazole</td>
<td>Linear IgA</td>
<td>ND</td>
<td>ND</td>
<td>Drug withdrawal, topical steroid</td>
<td>1 month</td>
<td>CR</td>
<td>4</td>
<td>Unknown</td>
</tr>
<tr>
<td>13</td>
<td>49/F</td>
<td>Multiple sclerosis</td>
<td>Tizanidine, Toltenamic acid</td>
<td>Linear IgA</td>
<td>ND</td>
<td>ND</td>
<td>Drug withdrawal</td>
<td>5 months</td>
<td>CR</td>
<td>4</td>
<td>Bullous pemphigoid</td>
</tr>
<tr>
<td>14</td>
<td>55/F</td>
<td>None</td>
<td>None</td>
<td>Linear IgA</td>
<td>ND</td>
<td>+</td>
<td>Dapsone</td>
<td>17 years</td>
<td>CR</td>
<td>N/A</td>
<td>Unknown</td>
</tr>
<tr>
<td>15</td>
<td>23/M</td>
<td>None</td>
<td>None</td>
<td>Linear IgA</td>
<td>ND</td>
<td>ND</td>
<td>Dapsone, prednisone</td>
<td>22 years (still active)</td>
<td>PR</td>
<td>N/A</td>
<td>Dermatitis herpetiformis</td>
</tr>
<tr>
<td>16</td>
<td>73/F</td>
<td>None</td>
<td>None</td>
<td>Linear IgA</td>
<td>ND</td>
<td>ND</td>
<td>Prednisone, dapsone</td>
<td>2 years</td>
<td>CR</td>
<td>N/A</td>
<td>Bullous pemphigoid</td>
</tr>
<tr>
<td>17</td>
<td>46/F</td>
<td>None</td>
<td>None</td>
<td>Linear IgA, C3</td>
<td>ND</td>
<td>ND</td>
<td>Prednisone, sulphapyridine, dapsone</td>
<td>3 years</td>
<td>CR</td>
<td>N/A</td>
<td>Eczema</td>
</tr>
<tr>
<td>18</td>
<td>23/F</td>
<td>None</td>
<td>None</td>
<td>Linear IgA</td>
<td>ND</td>
<td>+</td>
<td>Dapsone, prednisone, gluten-free diet</td>
<td>2 years</td>
<td>CR</td>
<td>N/A</td>
<td>Bullous pemphigoid</td>
</tr>
<tr>
<td>19</td>
<td>70/F</td>
<td>Coeliac disease, myelodysplastic syndrome, paroxysmal nocturnal haemoglobinuria</td>
<td>Linear IgA, C3</td>
<td>Linear IgA, C3</td>
<td>-</td>
<td>ND</td>
<td>Dapsone, prednisone, gluten-free diet</td>
<td>5 years (until death)</td>
<td>PR</td>
<td>N/A</td>
<td>Dermatitis herpetiformis</td>
</tr>
<tr>
<td>20</td>
<td>40/M</td>
<td>None</td>
<td>None</td>
<td>Linear IgA</td>
<td>ND</td>
<td>ND</td>
<td>Prednisone, dapsone</td>
<td>1 year</td>
<td>CR</td>
<td>N/A</td>
<td>Bullous dermatitis</td>
</tr>
<tr>
<td>21</td>
<td>73/M</td>
<td>None</td>
<td>None</td>
<td>Linear IgA, C3 &amp; weak IgG</td>
<td>ND</td>
<td>ND</td>
<td>Prednisone, azathioprine, Dapsone</td>
<td>3 years</td>
<td>CR</td>
<td>N/A</td>
<td>Dermatophytosis or bullous pemphigoid</td>
</tr>
<tr>
<td>22</td>
<td>71/M</td>
<td>None</td>
<td>None</td>
<td>Linear IgA</td>
<td>ND</td>
<td>ND</td>
<td>Dapsone</td>
<td>N/A</td>
<td>CR</td>
<td>N/A</td>
<td>Bullous dermatitis or acquired epidermolysis bullosa</td>
</tr>
<tr>
<td>23</td>
<td>36/M</td>
<td>None</td>
<td>None</td>
<td>Linear and granular IgA, IgG, and C3</td>
<td>ND</td>
<td>ND</td>
<td>Dapsone</td>
<td>N/A</td>
<td>CR</td>
<td>N/A</td>
<td>Eczema</td>
</tr>
</tbody>
</table>

IF: immunofluorescence; NS: Naranjo score; ND: not done; CR: complete response; +: positive; -: negative; PR: partial response (treatment effective but relapse of disease upon discontinuation), N/A: not applicable.
Direct immunofluorescence in all cases showed linear deposition of IgA at the BMZ. One patient had mixed IgA/IgG deposition, 2 patients an IgA/C3 deposition and 2 had a linear IgA/IgG/C3 deposition – one of these (No. 23) had granular deposition as well.

Indirect immunofluorescence was performed in 2 cases and in both of them was negative.

Six out of 16 adult cases were presumed to be drug induced (various antibiotics, fluconazole, NSAIDs, verapamil, digoxin, loperamide and metoclopramide). In 5 of 6 cases, 2 or more drugs were potentially involved. All patients went into remission after withdrawal of the culprit drugs and temporary treatment with topical or systemic corticosteroid. Mean duration of disease was 6 months (range 1–24 months, median 2.5 months). Mean age at disease onset in the drug-induced group was 66.5 years (range 49–79 years, median 66.5 years).

All patients with drug-induced LAD suffered from other diseases. One of the patients had bladder cancer as well as arteritis temporalis. Other concomitant diseases were diabetes, heart- and lung diseases, alcoholism, and multiple sclerosis.

One of the patients with idiopathic LAD (non drug-induced LAD) was diagnosed with coeliac disease, myelodysplastic syndrome and paroxysmal nocturnal haemoglobinuria.

Interestingly, 40% of the patients with idiopathic LAD, but none in the drug-induced group, showed a deposition of C3. Mean age at onset in the idiopathic group was 51 years (range 23–73 years, median 50.5 years), the F:M ratio was 1.0.

All the patients in the idiopathic adult group responded well to therapy with dapsone alone or in combination with prednisone. Two patients were initially treated with prednisone/azathioprine and prednisone/sulphasalazine, respectively, but were later on changed to monotherapy with dapsone. Mean duration of treatment in the idiopathic group was 6.9 years (range 1–22 years, median 3 years). Mean duration of treatment in the adult LAD group overall was 4.1 years (range 1 month–22 years, median 2 years). In most cases the duration of disease was relatively short but in 2 cases the patients needed continuous treatment to prevent relapse. Two recent cases were not included in these calculations since they just recently started treatment (cases 22 and 23). The typical doses used for the treatment of adult LAD were 0.5–1 mg prednisone kg/day and/or 50–150 mg dapsone/day. Four children and 2 adults were found to be HLA-B8 positive.

Incidence

In the 20-year period from 1994–2013 we found 16 incident cases of LAD (infant and adult form). The background population of our department is 1.2 million persons, which gives an incidence rate of 0.67/million/year.

DISCUSSION

We present the first larger case-series of Scandinavian patients with LAD, data which illustrates the heterogeneity of this disease.

An increasing incidence of LAD in our region is likely, as 7 patients were diagnosed in the first 22 years and 16 patients were diagnosed within the last 20 years. This finding may partly be due to a lack of diagnostic consensus in the 1970s and 1980s and partly due to a change in the referral pattern to our department. In 1994 the Danish disease-registration system was changed from ICD-8 to ICD-10 and the data retrieved prior to 1994 may be incomplete. Hence, the incidence rate calculation is based on data from 1994 until beginning of 2014. Patients may also be treated by local dermatologists and hence our incidence rate might be underestimated. The rate, though, is comparable to and even slightly higher than the incidence rates found in a German study: 0.23/million/year (7) and a French study: 0.49/million/year (8). In Kuwait, an age-adjusted incidence rate for CBDC of 2.3/million/year was found (9).

We have subdivided the adult LAD group into 2 groups with different characteristics: a drug-induced group and an idiopathic group.

The drug-induced cases represent 37.5% of the adult LAD cases in our series. These patients are generally older than idiopathic cases (mean age 66.5 years versus 51 years) and more likely they are of male gender (F:M ratio 0.5 versus 1.0). However, it must be kept in mind that the probability of receiving medications increase with age as does the probability of suffering from internal disease.

It is noticeable that one of our drug-induced cases showed deposition of both IgA and IgG at the BMZ. This is in contrast to an American study describing no deposition of IgG, although they found a weak deposition of C3 in 3 of 6 patients (10). None of our drug-induced cases exhibited C3 deposition. One child presented mixed IgA/IgG deposits while C3 was found only in the adult idiopathic group where it was present in 4 out of 10 patients. One patient (No. 23) had granular deposits of IgA along with the linear deposition, which made it impossible for the pathologist to differentiate between LAD and dermatitis herpetiformis. Hence, the diagnosis in the latter case was established based on the clinical characteristics, the lack of symptoms from the intestines, and a negative screening for coeliac disease. Mixed deposits are previously described in a number of cases (11–18). Their significance remains uncertain but it may be confusing and make the differential diagnosis more difficult.

It is always difficult to say whether a certain eruption is in fact caused by a certain drug although different algorithms exist to clarify this judgement, e.g. the Naranjo algorithm (19). We have applied the Naranjo algorithm for our suspected drug-induced cases, and the results
are listed in Table II. Only one of the 6 cases (No. 11) reaches the probability score of 5 meaning probable adverse drug reaction (ADR) due to one previous case report of penicillin as an inducer of LAD (20). The other 5 cases are assigned the probability score possible ADR.

In our opinion, a close time-relationship between drug introduction followed by the development of a rash, and disappearance of the rash upon drug withdrawal, support the suspicion that the rash is in fact induced by the drug. In our case-series 5 of 6 patients with suspected drug-induced LAD remitted within a few months (1–5) upon drug withdrawal. Amongst the idiopathic cases the mean duration of treatment was significantly longer: 6.9 years.

One of the suspected drug-induced cases was remitted only after 2 years, but in this case there was an association with bladder cancer as well, which previously has been described in association with LAD (21). As a consequence of the results above, we have chosen to differentiate between an idiopathic and a drug-induced group as described elsewhere in the literature (22). Recently, however, a review found no strong evidence that LAD is in fact induced by certain drugs, and the entity was questioned (23).

LAD has been described in association with malignancy as well as related to autoinflammatory conditions (for instance inflammatory bowel disease and Sjögren’s disease) (24–27). One of the patients with suspected drug-induced LAD was diagnosed with cancer of the bladder and one of the patients with idiopathic (non drug-induced) LAD was diagnosed with coeliac disease, myelodysplastic syndrome and paroxysmal nocturnal haemoglobinuria, associations that might be relevant.

The last mentioned patient had active skin disease until her death 5 years later. The patient with the longest disease duration (22 years), however, was otherwise completely healthy.

We found a slight male predominance (but not statistically significant) in our study in agreement with studies from Tunisia (28), Iran (29), North India (30) and Kuwait (9). Other studies from Poland and Tunisia, however, showed a slight female predominance (31, 32).

The mean age at disease onset for the children in our group was 2.7 years (range 11 months–4 years). This is a little lower than the ages reported in Tunisia: 5.5 years (33) and 7.5 years (28), North India: 3.5 years (30) and Kuwait: 6.8 years (9).

It is difficult to give a precise estimate of disease duration. Our patients were treated until remission and then, at some point, we started tapering the treatment. Sometimes a minor relapse occurred and dosing of treatment was increased. The mean treatment time for LAD in children at our department was 3.2 years (range 2–6 years, median 3 years). It is interesting, that the mean duration of disease in Tunisia is only 14 months (33) and in North India 8 months (30). A possible explanation for this phenomenon could be a shorter follow-up period in these studies.

In our department dapsone has been the drug of choice for LAD in adults, sometimes together with prednisone, to induce remission. In the childhood group half of the patients were initially treated with dapsone and half with sulphapyridine. None of these treatments seemed better than the other in our hands since 6 of 7 children underwent treatment with both drugs due to side effects or poor response and some patients were even treated with prednisone before remission occurred. In the literature, dapsone seems to be the drug of choice in both children and adults (9, 28, 30, 33–35).

Conclusion

LAD elicits a biphasic course affecting primarily young children and adults after their 5th decade. The disease is often mistaken for other bullous diseases such as impetigo (children) or bullous pemphigoid (adults). It is important to make the correct diagnosis, based on the clinical and immune histological findings, in order to provide the optimum treatment and care for the patient.

In general, dapsone must be regarded as the drug of choice for LAD. For childhood LAD, however, sulphapyridine seems to be just as effective and might be easier to administer. In some cases additional systemic corticosteroids are needed.

With an estimated incidence rate of 0.67/million/year in our region, LAD is a rare but benign condition that in most cases can be effectively treated.

The authors declare no conflict of interest.

REFERENCES