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Secondary Cushing’s syndrome in children with juvenile idiopathic arthritis following intra-articular triamcinolone acetonide administration

Sir, Intra-articular corticosteroid injection is a widely used treatment in the management of juvenile idiopathic arthritis (JIA) that generally induces rapid resolution of synovitis [1]. Triamcinolone hexacetonide (TH) is the preferred drug, with sustained symptom relief over longer periods than triamcinolone acetonide (TA) [2–4]. However, due to recent difficulties in obtaining TH, TA was used in our unit as an alternative agent. One hundred and ninety-five children (362 joints) and 180 children (216 joints) received intra-articular TH and TA, respectively, over a 3-yr period. Visibly prominent Cushing’s syndrome developed in nine (5%) of the children who had received TA. The clinical details are summarized in Table 1.

Table 1. Summary of clinical details for patients with cushingoid state after intra-articular injection

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Treatment</th>
<th>Joints (no.)</th>
<th>Total dose (mg)</th>
<th>Dose (mg/kg)</th>
<th>Summary of clinical details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>F</td>
<td>Extended oligoarthritis</td>
<td>None</td>
<td>6</td>
<td>100</td>
<td>4</td>
<td>Injection of knees, ankles and subtalar joints with TH. No complications observed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8</td>
<td>160</td>
<td>5</td>
<td>Injection of knees, ankles, subtalar and wrist joints with TA 2 yr later. Excessive weight gain and cushingoid appearance noted 2 weeks after injection</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>M</td>
<td>Enthesitis-related arthritis</td>
<td>Diclofenac 25 mg twice daily</td>
<td>4</td>
<td>180</td>
<td>5</td>
<td>Injection of left knee, ankle and both subtalar joints with TA. Cushingoid appearance noted 3 weeks after injection</td>
</tr>
<tr>
<td>3</td>
<td>12.9</td>
<td>M</td>
<td>Extended oligoarthritis</td>
<td>None</td>
<td>5</td>
<td>110</td>
<td>3.8</td>
<td>Injection of knees, ankles and left wrist with TH. No complications</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6</td>
<td>400</td>
<td>10</td>
<td>Injection of knees, ankles, left wrist and right elbow with TA 15 months later. Cushingoid appearance 3 weeks after injection</td>
</tr>
<tr>
<td>4</td>
<td>10.1</td>
<td>F</td>
<td>Polyarthritis RF negative</td>
<td>Methotrexate 10 mg weekly</td>
<td>6</td>
<td>240</td>
<td>14.5</td>
<td>Injection of knees, subtalar and elbow joints with TA. Cushingoid appearance observed 2 weeks after injection</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>F</td>
<td>Extended oligoarthritis</td>
<td>None</td>
<td>1</td>
<td>30</td>
<td>2.4</td>
<td>Injection of right knee with TA. No problems observed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>60</td>
<td>4.5</td>
<td>Injection of both knees with TA 4 months later. Cushingoid appearance observed 2 weeks after injection</td>
</tr>
<tr>
<td>6</td>
<td>15.5</td>
<td>F</td>
<td>Extended oligoarthritis</td>
<td>Prednisolone 10 mg once daily</td>
<td>1</td>
<td>80</td>
<td>2.3</td>
<td>Injection of left knee with TA. No complication</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4</td>
<td>240</td>
<td>6.5</td>
<td>Injection of hip, both wrists and left knee with TA 3 weeks later. She became cushingoid 2 weeks after injection</td>
</tr>
<tr>
<td>7</td>
<td>14.5</td>
<td>F</td>
<td>Extended oligoarthritis</td>
<td>None</td>
<td>1</td>
<td>80</td>
<td>1.4</td>
<td>Injection of left knee with TA without complications</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>160</td>
<td>2.8</td>
<td>Injection of both knees 6 months later. She became cushingoid 2 weeks after injection</td>
</tr>
<tr>
<td>8</td>
<td>5</td>
<td>F</td>
<td>Polyarthritis RF negative</td>
<td>Prednisolone 10 mg once daily</td>
<td>1</td>
<td>80</td>
<td>1.7</td>
<td>Injection of right knee. She became cushingoid after 4 weeks</td>
</tr>
<tr>
<td>9</td>
<td>6</td>
<td>F</td>
<td>Polyarthritis RF negative</td>
<td>Methotrexate 15 mg weekly</td>
<td>8</td>
<td>400</td>
<td>7.5</td>
<td>Injections of knees, wrists, ankles and shoulders. Cushingoid appearance still notable after 5 months</td>
</tr>
</tbody>
</table>
Intra-articular steroid injection is safe and effective in the management of JIA in children. Excessive weight gain and cushingoid appearance have been reported in adults and children following intra-articular TA injections but not with TH [5, 6]. Huppertz and Pfuller [7] reported transient suppression of endogenous cortisol release, detected by a low morning peak value of salivary cortisol, with no adverse events noted. Adrenocortical insufficiency was not formally assessed in our patient group. We did not observe a cushingoid state with TH even when multiple joints were injected, but accept that very minor weight gain or less prominent features, such as transient flushing of the cheeks, may not have been detected by this retrospective review. The development of a cushingoid state does not appear to be related to sex, age, current therapy or the type of arthritis. Although most of the children we reported had multiple intra-articular injections (up to eight joints at a time with a cumulative TA dose of up to 14.5 mg/kg). Cushing’s syndrome still occurred in three children who had only one or two joints injected (cases 5, 7 and 8). In our experience this side-effect was distressing for both carers and patients, although spontaneous resolution occurred, albeit over a variable period (no greater than 5 months in any patient). The resolution of hypercortisolism has been reported elsewhere to last up to 8 months [6]. We did not collect systematic data relating to the time of resolution in our patients, but none was greater than 5 months.

We undertook a separate study comparing the efficacy of 256 injections with TH and 113 with TA during the period when TH was unavailable, noting similar remission rates of 83% with TH and 87% with TA. Time to re-injections was 6.16 months with TA compared with 8.7 months for TH [8].

A cushingoid state is not uncommon after intra-articular administration of TA, including after injection of a single joint. Patients and carers should be counselled accordingly before treatment. We advocate TH as the therapy of choice because of its longer duration of action but, notwithstanding the adverse effect reported, our experience would support the use of TA as an effective alternative agent if TH is not available.

The authors have declared no conflicts of interest.

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Hepatomegaly as a rare presentation of Churg–Strauss syndrome

Sir, A 36-yr-old Caucasian female supermarket worker presented with increasing fatigue, dry cough, wheeze, drenching night sweats and weight loss. On examination she had multiple spider naevi and gross hepatomegaly. Investigation showed abnormal liver function tests with raised alkaline phosphatase 400 IU/l (31–116) and γ-glutamyl transferase 400 IU/l (0–72). Other liver function tests were normal, as were hepatitis, cytomegalovirus and human immunodeficiency virus serology. Strikingly, she had an eosinophilia of 10 × 10⁹/l with an erythrocyte sedimentation rate (ESR) of 95 mm/1st hour (0–15) and a C-reactive protein (CRP) of 40 mg/l (0–7). Computed tomography (CT) scanning showed hepatomegaly, the left lobe of the liver displacing the stomach, and hypoattenuation suggestive of periportal oedema with an enlarged lymph node in the porta hepatis (Fig. 1a); no other lymphadenopathy was seen on whole-body CT. All tumour markers, antinuclear and mitochondrial antibodies were negative.

There were no features of vasculitis or bacterial, fungal or tuberculous infections.

Churg–Strauss syndrome (CSS) was considered and a perinuclear antineutrophil cytoplasmatic antibody test (p-ANCA) was weakly positive, with proteinase 3 antibodies in low titre [12 IU/ml (0–10)] but a diagnosis of hypereosinophilic syndrome (HES) was felt more likely. Diagnostic criteria for HES [1] include the presents of persistent eosinophilia of 1.5 × 10⁹/l for longer than 6 months, lack of evidence for parasitic, allergic or other known causes of eosinophilia, and signs and symptoms of organ involvement. A significant percentage of HES patients have cryptic rearrangements of the PDGF receptor A gene, resulting in constitutive activation of this receptor with tyrosine kinase. These patients are sensitive to STI571 (Glivec), a tyrosine kinase inhibitor well known for its activity in chronic myeloid leukaemia. This patient did not have the gene rearrangement but her eosinophils were sensitive to STI571 so she was started on 400 mg daily.

There was, however, no improvement in her symptoms or eosinophilia, so she was referred to the St Thomas’ Hospital vasculitis clinic. Here her history revealed late-onset asthma and...