Is adrenal suppression in asthmatic children reversible?
A case series

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Background. Six hypocortisolaemic asthmatic children on steroids given at physiological doses were identified during a previous study. Objectives. To establish whether hypothalamic-pituitary-adrenal axis suppression (HPAS) could be reversed in hypocortisolaemic asthmatic children treated with steroids without sacrificing asthma control.

Methods. In this case series, treatment of six hypocortisolaemic patients was modified by introducing steroid-sparing asthma medications. Serum cortisol and repeat overnight metyrapone tests (ONMTPTs) were done until HPAS was reversed in all patients. A retrospective folder review was performed and the following data were extracted: body mass index standard deviation score (BMI SDS), adherence, daily steroid type and dose, treatment modification, serum cortisol, final ONMTPT result and time taken to achieve normalisation.

Results. The median serum cortisol level recovered to 311 nmol/L after 0.9 years (median). The ONMTPT normalised within 3.3 years (median). Steroid load decreased from 9.2 to 5.0 hydrocortisone equivalent mg/m²/d (medians), while asthma score improved from 1.42 to 0.85 (medians). Poor adherence was noted in two children before and four after treatment modification. BMI SDS decreased from ~0.08 to ~0.16 (medians).

Conclusions. Hypocortisolaemia and HPAS could be reversed in asthmatic children treated with physiological doses of steroids by reducing steroid load by 40% and supplementing therapy with steroid-sparing medication. Poor adherence may have either contributed to or retarded HPA recovery. Simultaneously, asthma control improved. Confirmation by a prospective study would be ideal, but may not be feasible.
Eight patients with hypocortisolaemia were identified during the previous year. Of these, one was lost to follow-up because of incorrect contact details. The remaining three boys and three girls (all of mixed ancestry) were followed up by the author (all retested patients were from Tygerberg Hospital). The median follow-up time was 503 days (range 3 - 30 months).

### Results

At diagnosis of hypocortisolaemia

<table>
<thead>
<tr>
<th>Patient</th>
<th>BMI SDS</th>
<th>Asthma score (%</th>
<th>FEV&lt;sub&gt;1&lt;/sub&gt; (%</th>
<th>Daily steroid type, dose (µg/m&lt;sup&gt;2&lt;/sup&gt;/d)</th>
<th>Adherence</th>
<th>BMI SDS</th>
<th>Asthma score</th>
<th>FEV&lt;sub&gt;1&lt;/sub&gt; (%)</th>
<th>Daily steroid type, dose (µg/m&lt;sup&gt;2&lt;/sup&gt;/d)</th>
<th>Adherence</th>
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<tbody>
<tr>
<td>1</td>
<td>0.87</td>
<td>0.86</td>
<td>130</td>
<td>ICS: 71  NS: 40  NS: BDP 205</td>
<td>Poor</td>
<td>1.19</td>
<td>0.71</td>
<td>105</td>
<td>Poor</td>
<td>ICS: BUD 325</td>
</tr>
<tr>
<td>2</td>
<td>1.76</td>
<td>2.86</td>
<td>79</td>
<td>ICS: 100  NS: 100  NS: BDP 81</td>
<td>Good</td>
<td>1.35</td>
<td>0.71</td>
<td>88.5</td>
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<tr>
<td>3</td>
<td>-0.10</td>
<td>0.83</td>
<td>n/a</td>
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<td>Poor</td>
<td>-1.05</td>
<td>1.14</td>
<td>n/a</td>
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<td>ICS: BUD 480</td>
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<tr>
<td>4</td>
<td>-0.06</td>
<td>4.14</td>
<td>54</td>
<td>ICS: 100  NS: 100  NS: BDP 243</td>
<td>Poor</td>
<td>0.07</td>
<td>0.85</td>
<td>74.8</td>
<td>Poor</td>
<td>ICS: BUD equiv 390</td>
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<tr>
<td>5</td>
<td>-0.54</td>
<td>1.00</td>
<td>65</td>
<td>ICS: 100  NS: 100  NS: BDP 209</td>
<td>Good</td>
<td>-0.39</td>
<td>n/a</td>
<td>n/a</td>
<td>Good</td>
<td>ICS: n/a</td>
</tr>
<tr>
<td>6</td>
<td>-1.40</td>
<td>1.42</td>
<td>80</td>
<td>ICS: 106  NS: 86  NS: BDP 88</td>
<td>Poor</td>
<td>-0.85</td>
<td>0.85</td>
<td>72.1</td>
<td>Poor</td>
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<tr>
<td>Mean</td>
<td>0.09</td>
<td>2.06</td>
<td>82</td>
<td>ICS: 88  NS: 78  NS: BDP 187</td>
<td>Poor</td>
<td>0.05</td>
<td>0.85</td>
<td>85</td>
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<tr>
<td>Median</td>
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<td>1.42</td>
<td>79</td>
<td>ICS: 93  NS: 207  NS: BDP 207</td>
<td>Poor</td>
<td>-0.16</td>
<td>0.85</td>
<td>82</td>
<td>n/a</td>
<td>ICS: BUD 316</td>
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</table>

### Discussion

At last follow-up

<table>
<thead>
<tr>
<th>Patient</th>
<th>BMI SDS</th>
<th>Asthma score</th>
<th>FEV&lt;sub&gt;1&lt;/sub&gt; (%)</th>
<th>Daily steroid type, dose (µg/m&lt;sup&gt;2&lt;/sup&gt;/d)</th>
<th>Adherence</th>
<th>Modifications</th>
</tr>
</thead>
<tbody>
<tr>
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<td>0.86</td>
<td>130</td>
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<tr>
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<td>1.76</td>
<td>2.86</td>
<td>79</td>
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<td>4.14</td>
<td>54</td>
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<td>DPI</td>
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<tr>
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<td>1.00</td>
<td>65</td>
<td>ICS: 100  NS: 100  NS: BDP 209</td>
<td>Good</td>
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<tr>
<td>6</td>
<td>-1.40</td>
<td>1.42</td>
<td>80</td>
<td>ICS: 106  NS: 86  NS: BDP 88</td>
<td>Poor</td>
<td>Formoterol</td>
</tr>
<tr>
<td>Mean</td>
<td>0.09</td>
<td>2.06</td>
<td>82</td>
<td>ICS: 88  NS: 78  NS: BDP 187</td>
<td>Poor</td>
<td>LA theophylline</td>
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<tr>
<td>Median</td>
<td>-0.08</td>
<td>1.42</td>
<td>79</td>
<td>ICS: 93  NS: 207  NS: BDP 207</td>
<td>Poor</td>
<td>ICS: BUD 316</td>
</tr>
</tbody>
</table>

BMI = body mass index; SDS = standard deviation score (based on Centers for Disease Control growth chart); FEV<sub>1</sub> = forced expiratory volume in 1 second; ICS = inhaled corticosteroids; NS = nasal steroids; BUD = budesonide; BDP = beclomethasone dipropionate; DPI = dry powder inhaler; LA = long acting.

*Range 1.7 - 7.1 years.
†Adherence <80% regarded as poor.
‡All on metered dose inhalers and spacers, patient 5 on prednisone 30 mg/d, patients 1, 3 and 4 treated with topical betamethasone with/without hydrocortisone.
§Based on patient's admission.
¶Asthma score calculated without FEV<sub>1</sub>, as it could not be established, excluded in calculation of mean/median.
||Mometasone furoate.
Patient 4's asthma control deteriorated on stopping HC, probably owing to poor adherence to ICS + NS therapy, necessitating a 3-day course of prednisone and an increase in the ICS dose. Patient 3 required a 5-day course of prednisone during an exacerbation, because the mother had discontinued the prescribed HC. Adherence to ICS + NS in this case was also poor, necessitating a second (3-day) course of prednisone, prolonged HC cover and increased ICS doses. Consequently, recovery of the axis took the longest in patients 3 and 4 (Table 2).

Patients 1, 3 and 4 were treated with topical betamethasone with or without HC for atopic dermatitis. Treatment modification in patients 1 and 3 consisted of methylprednisolone aceponate initially, followed by 10% diluted betamethasone ointment alternating with liquor picis carbonis. After modification, patient 4 only required emollients.

Serum cortisol normalised in all patients (Table 2). There was an adequate ACTH rise on the ONSMTPT in all except patient 4, where serum was insufficient. Normalisation of ACTH response can be inferred here, since the hypothalamus and pituitary are known to recover before the adrenal glands. Judging by the adequate 11DOC rise, these had recovered. The post-metyrapone 11DOC normalised in all except patient 3. A repeat test confirming total recovery was not considered necessary, because the supranormal ACTH response implied imminent recovery and the 11DOC result was approaching normality.

Discussion

Only one of the children presenting with hypocortisolaeemia was subjected to a supraphysiological daily steroid load. All others were treated with a total steroid dose equal to the daily physiological production rate, albeit in the upper range. When disregarding the NS contribution, the low ICS dose would generally be deemed safe. Hypocortisolaeemia has, however, been described in children being treated with doses as low as 200 µg beclomethasone dipropionate/day (2.5 mg HC equivalent) or 400 µg budesonide/day (5 mg HC equivalent). The suppressed cortisol production is balanced by the supply of exogenous steroids. Hypocortisolaeemia is one step away from adrenal crisis. When cortisol demand outstrips exogenous supply, as during an asthma exacerbation, an infection, surgery, injury or a burn, a crisis can be precipitated. As these stressors are usually unpredictable, HC replacement was prescribed as a precaution against a possible crisis. It also allowed for safe modification of asthma therapy. Furthermore, HC replacement was a protocol requirement, being essential therapy for hypocortisolaeemia.

After modification, the median steroid load of the group decreased by ~40%, leading to HPAS reversal in all cases. Instead of deteriorating, asthma control actually improved. In addition, the number of rescue prednisone courses required decreased considerably. The steroid/ non-steroid combination therefore appears to be superior in both safety and efficacy compared with the steroid-only therapy given by ~40%, leading to HPAS reversal in all cases. Instead of deteriorating, asthma control actually improved. In addition, the number of rescue prednisone courses required decreased considerably. The steroid/ non-steroid combination therefore appears to be superior in both safety and efficacy compared with the steroid-only therapy given by ~40%, leading to HPAS reversal in all cases. Instead of deteriorating, asthma control actually improved. In addition, the number of rescue prednisone courses required decreased considerably. The steroid/ non-steroid combination therefore appears to be superior in both safety and efficacy compared with the steroid-only therapy given
discontinued or reduced in two cases. A change in NS use is unlikely to have affected outcome, however, because median NS dosage actually increased. Secondly, the group’s BMI did not increase over time, implying that a BMI change is not likely to have contributed to recovery. Thirdly, although the assessment of adherence was limited by the different methods used before and after intervention, poor adherence could have contributed to the reversal in the two additional children known to have been poorly compliant after treatment modification. The reason for the poor adherence is not known, but is likely to be related to inadequate supervision due to the children’s advancing age. On the other hand, it also retarded recovery, as exacerbations necessitated prednisone courses and higher ICS doses, albeit intermittently. Furthermore, as airway diameter increases with age, airway narrowing is less severe, resulting in improved asthma control with subsequent lower ICS dose and recovery of the axis. However, while asthma was well controlled, dosages were reduced to lower steroid exposure and not because of improved symptoms.

Conclusions
In this case series, hypocortisolaemia developed in asthmatic children while all but one were being treated with steroid doses in the physiological range. On reducing the daily steroid load by ~40%, hypocortisolaemia and HPAS were effectively reversed in all. Poor adherence may have either contributed to or retarded HPA recovery. Simultaneously, asthma control improved. A prospective study would be ideal to confirm these findings, but may not be feasible.

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Author contributions
The author conceptualised and designed the case series and the study it is based on. He analysed and interpreted the data and wrote the article.

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Conflicts of interest
None.

References

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