Short report

The use of choline chloride in ataxic disorders

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SUMMARY Fourteen patients with a variety of ataxic disorders were given choline chloride, double blind for six weeks, in an attempt to improve gait and manual dexterity. One patient withdrew before receiving the active drug, twelve patients showed no functional improvement, but one achieved greater mobility; his response, which was dose dependent, ceased when choline was stopped and was reproducible.

At present there is no treatment available for cerebellar ataxia. Anticholinesterases produce a mild improvement in patients with a variety of spinocerebellar degenerations. Oral choline is said to increase rat brain choline and acetylcholine along with serum choline concentrations. Leggs tried this in a patient with idiopathic cerebellar ataxia. There was a clinical improvement; the anticholinesterase inhibitor physostigmine was ineffective and the response was blocked by anticholinergic drugs.

Patients and methods

Fourteen patients with predominantly cerebellar disability were selected (table). Weekly assessments were made by one observer. Patients and informants estimated progress and independence while walking, washing and feeding. Nystagmus and dysarthria were noted. Manual dexterity was assessed by spiral drawing, tapping in a circle, handwriting, pegboard time and hand tapping. Postural stability was measured with an ataxiometer, and walking speed timed over a constant distance.

After two baseline observations patients were randomly allocated to choline or placebo by a pharmacist. Neither patient nor doctor knew who was taking choline. Lemon flavoured choline chloride (1 g/5 ml) and placebo, containing quinine hydrochloride (250 mg/l) to imitate the bitter taste of choline, were prescribed weekly.

For the first three weeks the dose was 4 g/day followed by 150 mg/kg/day for the second three week period. After a one week interval the groups were reversed. Plasma choline concentrations were taken on the last day of each treatment period. The mean interval between last dose and sampling time was 5.2 hr with a range of 45 min to 18 hr. Blood was collected into precooled heparinised tubes; the plasma was selectively ultrafiltered at +4°C and the ultrafiltrate stored at −30°C. Plasma free choline was determined by radioenzymatic assay. Purified choline acetyltransferase (Chat EC No 2.3.1.6) was obtained from Sigma (London), and C14-acetyl coenzyme A (50 mCi/mmOL) from the Radiochemical Centre, Amersham.

Results

Three patients withdrew; case 5 because of a fractured hip, case 12 due to nausea on choline, and case 13 with transport difficulties, so that she did not receive the active drug.

Twelve patients reported no functional improvement, although two noticed minor changes. Case 3 reported improved mobility at home, and the boy with Friedreich's ataxia was less jerky (table).

Case 7 improved significantly in terms of mobility. He presented in 1975 with a nine month history of difficulty with balance, slurred speech and deteriorating handwriting. On examination he was dysarthric with a broad based gait, phasic nystagmus and an intention tremor of both upper limbs. Lumbar air encephalography showed cerebellar atrophy. At the start of the study he was...
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Table

Summary of patients in trial

<table>
<thead>
<tr>
<th>Case no</th>
<th>Initials</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Mobility</th>
<th>Average placebo score</th>
<th>Average choline score</th>
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<tbody>
<tr>
<td>1</td>
<td>DJ</td>
<td>38</td>
<td>M</td>
<td>Familial spino-cerebellar degeneration</td>
<td>Walks unaided</td>
<td>16</td>
<td>13</td>
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<tr>
<td>2</td>
<td>GT</td>
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<td>Walks unaided</td>
<td>22</td>
<td>18</td>
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<tr>
<td>3</td>
<td>CM</td>
<td>74</td>
<td>M</td>
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<td>Walks unaided</td>
<td>16</td>
<td>22</td>
</tr>
<tr>
<td>4</td>
<td>PF</td>
<td>10</td>
<td>M</td>
<td>Friedreich's ataxia</td>
<td>Walks unaided</td>
<td>41</td>
<td>18</td>
</tr>
<tr>
<td>5</td>
<td>AH*</td>
<td>64</td>
<td>M</td>
<td>Idiopathic cerebellar degeneration</td>
<td>Walks with a stick</td>
<td>53</td>
<td>27</td>
</tr>
<tr>
<td>6</td>
<td>FT</td>
<td>52</td>
<td>F</td>
<td>Mixed cerebellar and pyramidal signs</td>
<td>Walks unaided</td>
<td>34</td>
<td>81</td>
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<tr>
<td>7</td>
<td>HN</td>
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<td>Walks with a stick</td>
<td>67</td>
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<td>8</td>
<td>OS</td>
<td>60</td>
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<td>Walks unaided</td>
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<tr>
<td>9</td>
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<td>70</td>
<td>M</td>
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<td>Walks with a stick</td>
<td>16</td>
<td>22</td>
</tr>
<tr>
<td>10</td>
<td>JM</td>
<td>65</td>
<td>M</td>
<td>Alcoholic cerebellar degeneration</td>
<td>Walks with a stick</td>
<td>16</td>
<td>30</td>
</tr>
<tr>
<td>11</td>
<td>CO</td>
<td>63</td>
<td>M</td>
<td>Idiopathic cerebellar degeneration</td>
<td>Walks unaided</td>
<td>18</td>
<td>27</td>
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<tr>
<td>12</td>
<td>RG*</td>
<td>68</td>
<td>M</td>
<td>Mixed cerebellar and pyramidal signs</td>
<td>Walks with a stick</td>
<td>29</td>
<td>46</td>
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<tr>
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<td>Stands with support</td>
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<tr>
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<td>F</td>
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<td>Walks unaided</td>
<td>22</td>
<td>26</td>
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</table>

* Patient withdrew; choline results of low dose only.
NP Not possible.

Grouped hand function scores are an average of all tests of manual dexterity. These along with walking times produced consistent results throughout the trial period. Ataxiometer scores varied widely without demonstrating any overall trend. Spiral drawing and handwriting were difficult to quantify objectively. In all tests the highest score represents greatest disability.

just able to walk with the aid of a stick. After 10 days treatment he and his wife noted better mobility. The higher dose of choline produced an enhanced response although he still required a stick for stability. Ataxiometer and grouped hand function scores showed a moderate improvement (figure). Within 10 days of stopping choline he noted a deterioration. At three weeks his walking time and grouped hand function scores had doubled. Choline was restarted at 150 mg/kg/day. Over the following three weeks results improved similar to those achieved initially. (Ataxiometer scores are not available for this period.) His plasma choline concentrations were: on placebo

Figure Changes in hand function, stance and gait in Case 7 during placebo and choline therapy.
10.7 μmol/l, choline low dose 12.8 μmol/l, high dose 36.1 μmol/l.

Side effects of choline included nausea and diarrhoea on the higher dose. The characteristic "bad fish" body odour was noted in five patients. Blood pressure and weight were unchanged.

On placebo, choline concentrations ranged from 8.2 to 23.0 μmol/l (12.0 ± 0.96, mean ± SEM). At 4 g/day levels choline concentrations increased to between 9.5 and 27.7 μmol/l (17.8 ± 1.77, mean ± SEM), and at 150 mg/kg/day concentrations rose to between 21.0 and 43.8 μmol/l (31.9 ± 2.42, mean ± SEM; a 166% increase; p<0.001 by Student's t-test). No significant reduction in the choline content of the prescribed solutions was found when assayed after six weeks storage at +4°C.

**Discussion**

Choline is the rate limiting substrate for the synthesis of acetylcholine in cholinergic nerves. The basis for any therapeutic effect and its site of action in ataxic disorders are not understood. Any improvement raises the possibility of a deficient cholinergic mechanism in this group.

There are particular difficulties in studying the effect of a drug in cerebellar disability. Manual dexterity tests generally improve with practice. Measurements of handicap are hard to quantify and may vary considerably from one observation to the next. Patients with chronic disorders sometimes derive a psychological boost from interest taken in them during the course of a clinical trial and naturally rest hope in the new remedy. In addition choline produces a characteristic body odour which if recognised may prejudice the results.

Case no 7's results may be genuine: all criteria showed improvement, walking time improved incrementally with increased dose, withdrawal of choline produced a relapse, and re-introduction a further response. However, run-in and placebo periods showed a variable baseline, and order effects or chance improvement cannot be excluded in a single trial.

Plasma choline concentrations recorded make it unlikely that we missed a therapeutic response through inadequate dosage, differences in absorption or rates of metabolism. The patient who responded improved to an extent at the lower dose and his plasma choline concentrations correspond with those that achieved a 55% increase in rat cerebellar acetylcholine concentrations experimentally.6

Choline appears to have had no effect in cerebellar ataxia with one possible exception. However, in such a heterogenous group any response is likely to be patchy; even patients with idiopathic cerebellar degeneration may turn out to have more than one biochemical derangement. A truly blind study with choline is not possible but this might be realised using lecithin7 and repeated cross-overs. Even the occasional response would justify a trial of treatment in this distressing and intractable clinical situation, particularly when side effects are minimal.

We thank Mr Steven Nice, Staff Pharmacist, Leicester Royal Infirmary for his help in this study.

**References**

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