A new approach: Valproic acid in Huntington’s Disease.  
Dose dependent improvement of myoclonic hyperkinesia: an Open-Label, Observational Study in a subgroup.

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Abstract

Background: Huntington’s Disease (HD) is characterized by choreatic movements. Chorea is treated with antidopaminergic neuroleptics like tiaprid and tetrabenazine. Especially in patients with signs of parkinsonism antidopaminergic medication often leads to a worsening of symptoms. In earlier studies valproic acid showed no beneficial effect on involuntary movements. Myoclonus is rare in HD and often overseen or misdiagnosed as chorea. It does not sufficiently respond on antidopaminergic medication.

Methods: In this report we present eight patients suffering from myoclonic hyperkinesia as the main symptom. All patients were treated with valproic acid and scored by using UHDRS motor score before and after treatment. Two patients accepted to be additionally videotaped.

Results: In seven patients myoclonus and, therefore, UHDRS motorscore improved in a dose dependent manner. In three of these patients antidopaminergic medication could be reduced.

Conclusions: In the rare subgroup of HD patients suffering from myoclonus valproic acid is a possible alternative. Valproic acid seems to be more efficient than antidopaminergics in those patients. Besides, valproic acid has no side effects on the extrapyramidal system.

Background

Huntington’s disease (HD) is an autosomal dominantly transmitted neurodegenerative disorder based on expansions of translated CAG repeats in the huntingtin gene beyond a threshold of 36 to >200 units. The characteristic motor feature of HD is chorea, but parkinsonism and involuntary movements such as dystonia and myoclonus can also be present. Choreatic movements usually are treated with antidopaminergic neuroleptics like tiaprid and tetrabenazine. Especially in patients with signs of parkinsonism, however, antidopaminergic medication often leads to a worsening of symptoms. Dopaminergic drugs or even low-dose levodopa can be administered in patients with the akinetic rigid juvenile variant of HD. Myoclonus is a rare feature of HD. It does not sufficiently respond on antidopaminergic medication. A few reports of myoclonus in HD have mainly concerned cases of juvenile onset [1-3]. Earlier studies using valproic acid in HD did not show a beneficial effect on involuntary movements particularly with regard to choreatic hyperkinesias ([4] 2 patients; [5, 6] 5 patients; [7] 14 patients; [8] 8 patients; [9] 3 patients; [10] 1 patient). On the other hand, few case reports describing myoclonus in HD, report about an improvement of movement disturbances after administration of valproic acid or other medication than antidopaminergics. Carella et al. described a patient with adult onset HD and prominent action myoclonus. Treatment with valproic acid greatly reduced myoclonus suggesting that the gamma-aminobutyric acid (GABA) system might be involved in the pathophysiology of myoclonus in HD [11]. In another case report two brothers with clinically definite adult Huntington’s disease developed disabling
myoclonus years after the first signs of the disease, which could be controlled with valproic acid [12]. Thompson et al. describe three patients with HD presenting symptoms before the age of 30, with myoclonus as the predominant clinical feature. The myoclonus improved with piracetam therapy in one patient and a combination of valproic acid and clonazepam in the others [13]. Two further case reports describe an improvement in cases of severe intention myoclonus by clonazepam in adult HD [14, 1]. Funakawa et al. report on a cortical reflex myoclonus in adult onset HD. Oral administration of clonazepam was transiently effective for myoclonus [15]. Apart from this, valproate has also been reported to be effective as a mood stabilizer in HD [16].

We herein describe eight adult HD patients who suffered from severe action myoclonus or myoclonic hyperkinesia leading to physical disability. All patients were treated with valproic acid. To our knowledge, this is the largest collective of this rare feature reported so far.

Methods
About 90% of 600 HD patients investigated in our center during the last 10 years showed symptoms of chorea, about 60% suffered from choreatic movements as the main somatic symptom. Eight patients suffered from myoclonus as the main clinical symptom and were treated with valproic acid. Patients were scored by Unified Huntington’s Disease Rating Scale (UHDRS) motor score before and after treatment with valproic acid [17, 18]. Two patients accepted to be videotaped initially and after treatment with valproate. One patient was able to give a handwriting test initially and after treatment with valproic acid. If possible peg insertion was performed during treatment in order to evaluate executive dysfunction and motor impairment [19, 20]. All patients had been genetically tested and were symptomatic for HD with choreatic hyperkinesia. Additionally, all patients showed signs of akinesia and rigidity, most of them also suffered from dysphagia. Myoclonus, however, was the predominant clinical symptom. All patients demonstrated a worsening of myoclonus during action, some did also present severe myoclonic hyperkinesias at rest (case 1, 3, 4, 7 and 8). One patient (Case 3) had been treated with valproic acid due to seizures before first investigation (1050 mg/per day, serum level: 31 µg/ml) but the dose had to be increased during treatment. The same patient (listed as case 4) was readmitted 4 years later because of worsening of the symptoms and was treated again by increasing the valproic acid medication (Initial dose 1800 mg, serum level: 37 µg/ml). Characteristica of all patients are described in table 1.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>CAG AO</th>
<th>Motonic AO</th>
<th>Psych AO</th>
<th>Duration</th>
<th>Initial TFC</th>
<th>Initial IS %</th>
<th>Rigidity</th>
<th>Swallowing problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>M</td>
<td>22/46</td>
<td>28</td>
<td>22</td>
<td>11</td>
<td>2</td>
<td>20</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Case 2</td>
<td>F</td>
<td>20/54</td>
<td>37</td>
<td>ND</td>
<td>6</td>
<td>5</td>
<td>70</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Case 3*</td>
<td>M</td>
<td>17/48</td>
<td>23</td>
<td>23</td>
<td>8</td>
<td>3</td>
<td>40</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Case 4*</td>
<td>M</td>
<td>17/48</td>
<td>23</td>
<td>23</td>
<td>12</td>
<td>2</td>
<td>30</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Case 5</td>
<td>M</td>
<td>19/48</td>
<td>33</td>
<td>ND</td>
<td>11</td>
<td>4</td>
<td>40</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Case 6</td>
<td>M</td>
<td>17/43</td>
<td>50</td>
<td>45</td>
<td>6</td>
<td>3</td>
<td>40</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Case 7</td>
<td>F</td>
<td>25/52</td>
<td>31</td>
<td>ND</td>
<td>10</td>
<td>3</td>
<td>40</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Case 8</td>
<td>F</td>
<td>17/50</td>
<td>28</td>
<td>26</td>
<td>7</td>
<td>6</td>
<td>70</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Case 9</td>
<td>M</td>
<td>17/50</td>
<td>30</td>
<td>30</td>
<td>11</td>
<td>3</td>
<td>30</td>
<td>+++</td>
<td>+++</td>
</tr>
</tbody>
</table>

Table 1
Clinical data of all patients with valproic acid. AO= age of onset, TFC= Total functional capacity (UHDRS), IS= Independence score (UHDRS), CAG= CAG-ranges (low/high). Swallowing problems (=none, +=mild, ++=moderate, +++=severe). ND= no data. One patient (*) was treated twice with an increasing dosage of valproic acid within an interval of 4 years, see text.
Results
In seven patients (8 cases) myoclonic hyperkinesias and, therefore, UHDRS scores improved in a dose dependent manner (see table 2). Initial mean UHDRS motor score was 73.1 (±11.9), after treatment mean UHDRS motor score was 60.2 (±12.8) for all patients (p=0.042; t-test; data showed a normal distribution according to the Kolmogorov-Smirnow test) due to an improvement in overall motor function. In three of these patients antidopaminergic medication could be reduced markedly (case 4, 7 and 8), in the remaining patients antidopaminergic treatment was basically unchanged (table 2). Especially in case 1 and 4 swallowing improved. One patient with a daily dose of only 300 mg valproate did not improve. Changes in comedication during treatment are demonstrated in table 2.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Initial UHDRS</th>
<th>Second UHDRS</th>
<th>Valproic acid (mg/day)</th>
<th>Valproic acid serum level (µg/ml)</th>
<th>Mood stabilisation</th>
<th>Improvement of mobility and skillfulness</th>
<th>Changes in comedication in mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>80</td>
<td>72</td>
<td>900 mg</td>
<td>30 µg/ml</td>
<td>+++</td>
<td>+</td>
<td>T↓↓100 CBZ↑900 MEL↓37.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TE⇔, LO⇔, CL↓25</td>
</tr>
<tr>
<td>Case 2</td>
<td>65</td>
<td>33</td>
<td>1200 mg</td>
<td>87 µg/ml</td>
<td>-</td>
<td>+++</td>
<td>R⇔</td>
</tr>
<tr>
<td>Case 3*</td>
<td>79</td>
<td>61</td>
<td>1800 mg</td>
<td>59 µg/ml</td>
<td>+</td>
<td>+</td>
<td>T↓↓100 CL↓44 CLO↓0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LEV↓1000 TE⇔ CBZ↑1400</td>
</tr>
<tr>
<td>Case 4*</td>
<td>84</td>
<td>74</td>
<td>2700 mg</td>
<td>43 µg/ml</td>
<td>++</td>
<td>++</td>
<td>T↓↓300 TE↓25 CLO↓0.5 CL⇔</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CBZ↑1400</td>
</tr>
<tr>
<td>Case 5</td>
<td>56</td>
<td>56</td>
<td>300 mg</td>
<td>(ND)</td>
<td>-</td>
<td>-</td>
<td>T⇔, TE⇔, LO⇔, OX⇔, HAL⇔</td>
</tr>
<tr>
<td>Case 6</td>
<td>72</td>
<td>66</td>
<td>900 mg</td>
<td>73 µg/ml</td>
<td>++</td>
<td>+</td>
<td>T⇔, HAL⇔</td>
</tr>
<tr>
<td>Case 7</td>
<td>74</td>
<td>60</td>
<td>1050 mg</td>
<td>43 µg/ml</td>
<td>+++</td>
<td>++</td>
<td>T↓↓150 TE↓25 S↓200 Q⇔</td>
</tr>
<tr>
<td>Case 8</td>
<td>57</td>
<td>50</td>
<td>1950 mg</td>
<td>84 µg/ml</td>
<td>+</td>
<td>+++</td>
<td>T↓↓300 LO⇔1.5</td>
</tr>
<tr>
<td>Case 9</td>
<td>91</td>
<td>70</td>
<td>1350 mg</td>
<td>56 µg/ml</td>
<td>++</td>
<td>++</td>
<td>T↓↓50 LO⇔, Q⇔, MEL⇔</td>
</tr>
</tbody>
</table>

Table 2
Clinical data and comedikation before and after treatment with valproic acid. ND= no data, (−=no, +=mild, +++=moderate, +++=very good). T=Tiaprid, TE=Tetramezine, CBZ=Carbamazepine, CL=Clozapine, CLO=Clonazepam, MEL=Melperone, LO=Lorazepam, R=Rilutek, LEV= Levetiracetam, OX= Oxazepam, HAL=Haloperidol, S=Sulpride, Q=Quetiapin. One patient (*) was treated twice with an increasing dosage of valproic acid within an intervall of 4 years, see text.
In five cases a remarkable mood-stabilizing effect of valproic acid could be observed. In case 2 due to treatment with valproic acid myoclonic hyperkinesia improved very much. Especially mobility and skilfulness of the hands were ameliorated, this could be demonstrated by writing tests (see picture 1 without, picture 2 with 900 mg, picture 3 with 1200 mg valproic acid). For this patient performance of peg insertion initially and with treatment of 600 mg valproic acid was not possible. After treatment with 1200 mg valproic acid peg insertion was possible, but still showed high values (3196 ms right hand, 4813 ms left hand). Videotapes were performed initially and after treatment with valproic acid (see video 1 without and video 2 with 900 mg valproic acid for case 1, video 3 without and video 4 with 1950 mg valproic acid for case 8). No relevant side effects were observed.

Conclusions
Due to specific degeneration of striatal neurons juvenile and rigid HD patients react early with a development of extrapyramidal side effects after antidopaminergic therapy. Moreover, not only hyperkinetic involuntary movements but also bradykinesia has been increasingly recognized as one of the key symptoms in non-juvenile HD-patients also in early stages of the disease [21-23]. Therefore, antidopaminergic medication often leads to a worsening of swallowing problems and gait disturbances. In a subgroup of HD patients suffering from myoclonic hyperkinesia valproic acid may be a possible alternative treatment. Valproic acid seems to be more efficient than antidopaminergics in those patients. Besides, it has no side effects on the extrapyramidal system in opposite to neuroleptics. In some of our cases reduction of antidopaminergic medication was possible with an improvement of bradykinesia and swallowing. These effects seem to be dose dependent as demonstrated in case 2, 3 and 4. In case 2 writing tests show a remarkable improvement after an increase of dosage (see pictures 1-3). Because of worsening of symptoms one patient (listed as case 3 and 4) was treated twice within an interval of 4 years. An improvement of symptoms could be reached each time after increasing the dosage of valproic acid, this might be a further hint for dose dependent effects. Only one patient (case 5) with a daily dose of only 300 mg valproic acid did not improve. This might be due to underdose. For all other patients the reduction of disabling myoclonus led to a significant improvement in activity of daily living. Almost all patients developed initial HD symptoms early in life (AO 23 years up to 33 years) but none of them was a juvenile HD patient with characteristic akinesia and rigidity. Myoclonus appeared 6 to 12 years after AO of first symptoms of the disease in all patients. All patients had an expanded CAG range between 45 and 50. There seems to be a subgroup of patients between those with typical choreatic movements and those with the juvenile akinetic-rigid subform. As Carella et al. postulated the gamma-aminobutyric acid (GABA) system might be involved in the pathophysiology of myoclonus in HD [11]. Earlier animal models with stereotaxic injection of kainic acid into rat striatum produced neuronal degeneration and neurochemical alterations resembling HD [24]. Since that it was assumed that correction of the deficiency in gamma-aminobutyric acid (GABA) in HD may be of therapeutic value. Furthermore, there are some reports suggesting a neuroprotective role of valproate, acting as a histone deacetylase-Inhibitor. Thus, valproic acid seems to be a promising candidate for a new approach in Huntington’s Disease [25-34].
**Picture 1**
Case 2 handwriting test without vaproic acid treatment.

**Picture 2**
Case 2 handwriting test with 900 mg vaproic acid treatment.

**Picture 3**
Case 2 handwriting test with 1200 mg vaproic acid treatment.

**Video 1**
Case 1 without vaproic acid treatment.

**Video 2**
Case 1 with 900 mg valproic acid treatment.

**Video 3**
Case 8 without vaproic acid treatment.

**Video 4**
Case 8 with 1950 mg valproic acid treatment.

**Competing interests:**
The author(s) declare that they have no competing interests.

**Acknowledgement:**
Written consent was obtained from the patient or their relative for publication of videotape. We thank all patients participating in this study.

**Authors’ contributions:**
CS has made substantial contributions to conception and design and acquisition of data. TL made substantial contributions to acquisition of data; PK to analysis and interpretation of data; HP revising it critically for important intellectual content; JA has been involved in acquisition of data, drafting the manuscript and has given final approval of the version to be published.

**References:**


Heute ist so süß!
Heute ist ein schöner Tag.
Additional files provided with this submission:

Additional file 4: Video4 case8 valproic acid 1950 mg.mpg: 10106Kb
http://www.biomedcentral.com/imedia/1958066185750166/sup4.MPG

Additional file 3: Video3 case8 no valproic acid.mpg: 7410Kb
http://www.biomedcentral.com/imedia/9598603167501660/sup3.MPG

Additional file 2: Video2 case1 valproic acid 900 mg.mpg: 6552Kb
http://www.biomedcentral.com/imedia/7777286097501660/sup2.MPG

Additional file 1: Video1 case1 no valproic acid.mpg: 7022Kb
http://www.biomedcentral.com/imedia/1609118115750166/sup1.MPG