First use of creatine hydrochloride in premanifest Huntington disease

Huntington disease is a devastating autosomal dominant neurodegenerative disorder that typically manifests between ages 30 and 50 years. Promising high-dose creatine monophosphate trials have been limited by patient tolerance. This is the first report of use of creatine hydrochloride in two premanifest Huntington disease patients, with excellent tolerability over more than 2 years of use.

Clinical record

A 33-year-old patient in our general practice carried the autosomal dominant gene for Huntington disease (HD). The abnormal number of cytosine-adenine-guanine triplet repeats in the huntingtin gene she carried meant she would eventually become symptomatic for this dreadful disease.

The patient requested information regarding potential treatments, as she had become aware of clinical trials for HD and of compounds used by patients with HD. A neurologist had previously recommended a healthy diet, exercise, avoiding excessive toxins (such as alcohol), social enrichment and cognitive stimulation, which together may modestly slow clinical disease progression and improve quality of life.[1] She had used preimplantation genetic diagnosis during her pregnancies but preferred otherwise not to focus on her condition. She understood that there were no proven therapies for this incurable condition and did not want to attend HD clinics. She was asymptomatic.

At her request, I searched the PubMed database for possible treatment options. There were some that were unproven in HD but had been used safely in humans for other indications, had a reasonable rationale regarding known HD pathophysiology, and had positive results in animal models of HD and/or early-phase human HD trials.[2]

In January 2012, I sought advice on using these options (eg, high-dose creatine, melatonin, coenzyme Q10, trehalose, ultra-low-dose lithium with valproate) from a specialist HD clinic but was advised against this approach. Instead, it was suggested that the patient might be able to sign up for clinical trials including high-dose creatine. The patient chose subsequently to participate in an observational trial (PREDICT-HD) which did not limit her options. However, she declined consideration for the Creatine Safety, Tolerability, and Efficacy in Huntington's Disease (CREST-E) study,[3] an international Phase III placebo-controlled trial of creatine monophosphate (CM) in early symptomatic HD. It is also very unlikely she would have been accepted for this trial as she was asymptomatic.

In February 2014, the Creatine Safety and Tolerability in Premanifest HD trial (PRECREST),[4] a Phase II trial, showed significant slowing of brain atrophy in CM-treated premanifest HD patients. If convincingly replicated, this would be a major advance.

The main practical problem with high-dose CM (20–30 g daily) is tolerability. Adverse effects are common, especially nausea, diarrhoea and bloating. In people who have normal renal function before commencing creatine supplementation, creatine does not appear to adversely affect renal function.[5]

In PRECREST, about two-thirds of patients tolerated the maximum dose (30 g daily) and 13% of those on placebo were unable to tolerate CM when they switched to it. Moderate intolerance appears to be common. A high drop-out rate affected the HD gene carriers in this study despite assumed high motivation.[6] Recommended additional water intake for patients on CM therapy is 70–100 mL per gram of creatine per day, which is problematic at high doses of CM.

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The patient again requested assistance as she wanted to seek the best available potential treatment to face her condition with equanimity.[7] I decided that, provided safety was paramount, I would assist her on an informed consent basis as part of my duty of care, respecting her informed autonomy.

A case presentation and treatment plan was prepared and an expert team of relevant medical specialists was assembled. Comprehensive informed written consent, including consent from the patient's partner for additional medicolegal protection, was obtained. The New South Wales off-label prescribing protocol[8] was followed, actions were consistent with article 37 of the Declaration of Helsinki,[9] and medical defence coverage for the proposed treatment was specifically confirmed by my indemnity insurer.

After baseline assessment, including renal function and careful attention to hydration, the patient commenced oral CM therapy at 2 g/day. This was slowly increased to 12 g/day but she was unable to maintain this dosage due to gastrointestinal adverse effects.

Creatine hydrochloride (CHCl), a creatine salt that has greater oral absorption and bioavailability than CM, and requires less water and a lower dose, offered a possible solution.[10] The reduced dose also reduces intake of contaminants, which is very important for extended use. Use

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of CHCl has been confined to the bodybuilding industry and, to the best of my knowledge after a careful search of PubMed, nothing has previously been published in the context of neurodegenerative disorders.

After review by a pharmacologist and consultation with the co-inventor of the available formulation of CHCl,[10] a daily dose of 12 g (equivalent to about 19 g CM) with 100 mL water per 4 g of CHCl was proposed. The manufacturer (AtroCon Vireo Systems) provided 1 g capsules of pharmaceutical grade CHCl at reduced cost. The patient decided to commence CHCl therapy after ceasing CM therapy. The dose of CHCl was slowly increased to 4 g three times a day (12 g daily) with a minimum of 100 mL additional fluid per 4 g dose.

The patient has been taking this dosage since January 2013 without any significant adverse effects and is keen to continue. Her serum creatinine levels are stable. Her serum creatine levels before and after doses have also been measured, and this confirmed that the CHCl is being absorbed.

Shortly after this patient began CHCl therapy, a second related premanifest HD patient requested access to CHCl. After a similar informed consent process, the second patient commenced the same dose of CHCl and has also not developed significant adverse effects. Clinically, both patients remain well.

Discussion

This is the first report of CHCl use in HD, with excellent tolerability for more than 2 years by two patients. If replication of the PRECREST findings confirms high-dose creatine as the first potentially disease-modifying treatment for HD, CHCl may represent an important option for patients, warranting further studies.

In this context, it is disappointing that CREST-E was closed in late 2014 after interim analysis showed it was unlikely to show that creatine was effective in slowing loss of function in early symptomatic HD based on clinical rating assessment to date. There were no safety concerns.[11]

It will be interesting to see, when eventually analysed and published, whether the magnetic resonance imaging (MRI) data from CREST-E showed any benefit in any subgroup and whether the trial cohort as a whole were in fact all in early-stage disease, and to consider whether the clinical rating scales were sensitive enough in this specific trial context.

Although others disagree, I argue that it remains unclear based on PRECREST findings whether the lack of benefit of creatine for early *symptomatic* disease in CREST-E is strictly relevant to the much earlier presymptomatic stage of the disease, especially when patients are far from onset.

HD symptoms take 30–50 years to develop, and the disease generally progresses to early dementia and death. Progressive MRI abnormalities accumulate for 20 or more years before onset. It appears that by the time the disease becomes symptomatic after 30–50 years, a multiplicity of interacting pathogenic mechanisms have become active (eg, excitotoxicity, mitochondrial energy deficit, transcriptional dysregulation, loss of melatonin receptor type 1, protein misfolding, microglial activation, early loss of cannabinoid receptors, loss of medium spiny striatal neurones, oxidative stress), and early and late events have occurred. The authors of a study of postmortem HD brain tissue refer to these mechanisms as a "pathogenetic cascade",[12] while others refer to them as multiple interacting molecular-level disease processes.[13] "Early" downregulation of type 1 cannabinoid receptors has been identified as a key pathogenic factor in HD.[14] In a recent review on the pathophysiology of HD, the authors described "a complex series of alterations that are region-specific and time-dependent" and noted that "many changes are bidirectional depending on the degree of disease progression, i.e., early versus late".[15] These and other findings suggest that HD has a *complex temporal and mechanistic evolution* that has not been fully elucidated. For this reason, we should think carefully before abandoning an agent when it fails at the relatively late symptomatic stage of this devastating and incurable disease.

As creatine is thought to have a useful potential for action in relation to only *one* of the many relevant disease mechanisms — mitochondrial energy deficit — was it too much to expect creatine to have a significant impact on symptomatic-stage disease in CREST-E? It seems possible, based on the references cited above, that there are fewer (or less intense) pathogenic mechanisms operating at much earlier presymptomatic stages of the disease, when the brain is more intact and plastic. If so, treatment trials in presymptomatic patients assessed using MRI or other biomarkers might offer better prospects for benefit.

I believe that sophisticated replication of PRECREST (or at least clarification as to whether the slowed rate of atrophy on MRI in premanifest patients was genuine or artefactual) is an ethical obligation that we owe to the HD community who contributed so much to CREST-E.

There are significant ethical and sociomedical issues associated with HD research. In reviewing the literature, it was obvious that early-phase research contains multiple examples of existing, out-of-patent or non-patentable potential therapies that appear to warrant modern clinical trials and, I argue, at an appropriate early stage of the disease.[2,16,17] Early-phase studies of combination therapies with existing agents appear frequently to receive little, if any, follow-up.[2,18]

Currently, any drug for which US Food and Drug Administration or European Medicines Agency approval is sought for presymptomatic HD must achieve a clinical end point first in symptomatic HD, then requalify in presymptomatic HD, meeting combined clinical and biomarker end points. Does this arbitrarily overprivilege the clinically observable stage of a disease, which is now understood (based on relatively recent MRI studies) to have a course of 20 or more years before symptoms begin?

Because of the enormous costs associated with drug development, and the uncertainty of such research, I

believe that it is time for a renewed focus on small, targeted clinical trials, especially in premanifest HD, using existing and novel agents. Recent advances in MRI and additional biomarkers that are under development[19] open the possibility of meaningful small trials that aim to slow HD progression until gene therapy arrives.

None of this, however, will achieve its full potential unless we address the barriers to genetic testing. The true incidence of many genetic conditions, including HD, in Australia is unknown. If a treatment becomes available, more people will want to be tested. The decision to have genetic testing is complex, controversial and uniquely personal. Respecting this, I believe that we need to urgently follow the lead of the United States, Germany, Sweden, France, Denmark and other countries in legislating to end genetic discrimination in health, insurance, employment and services.[20] I urge policymakers to replicate and clarify PRECREST and, in full collaboration with the HD community, trial existing and available medications alongside novel agents.

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