Hydrocephalus Complicating Intrathecal Antisense Oligonucleotide Therapy for Huntington's Disease

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Huntington's disease (HD) is a genetic disorder caused by an expanded CAG repeat in the *huntingtin* gene, and although there are currently no disease-modifying treatments, there is much excitement about the prospect of treatments targeting huntingtin expression. In a phase I/2A trial of an antisense oligonucleotide (ASO) treatment (Tominersen), no serious adverse events were recorded, and there was a dose-dependent reduction in cerebrospinal fluid (CSF) huntingtin levels[1]. In an open-label extension (OLE) study, patients received monthly or bimonthly Tominersen, with preliminary data confirming the reduction in mutant huntingtin levels[2]. Here we report on a unique major adverse effect occurring during this OLE.

A 54 year old man with a pathogenic *huntingtin* CAG repeat of 42, received monthly intrathecal Tominersen during the OLE, having received four doses of intrathecal placebo during the prior phase I/2A trial. At the start of the OLE he had modest chorea and broken ocular pursuit, with a total Unified Huntington's Disease Rating Scale (UHDRS) motor score of 12. His mobility was normal, and he performed tandem gait without support, and he was still working.

Following his fifth monthly dose of Tominersen, he developed gait difficulties, with an unsteady broad-based gait along with mild finger-nose and heel-shin ataxia, and an inability to perform a tandem gait. He initially continued to receive monthly Tominersen, but his gait deteriorated over the following three months and he started to fall, and could no longer work. His UHDRS motor score increased to 38.

His clinical deterioration was accompanied by a progressive rise in CSF protein, peaking at 2.64 g/l, and a CSF lymphocytosis, peaking at 46 cells/mm^3 (Figure 1A and 1B). Serial brain MRI revealed increasing ventricular dilation, with periventricular oedema, consistent with hydrocephalus (Figure 1C and 1D). His gait improved dramatically following a high-volume CSF tap, and lumbar infusion studies confirmed increased resistance to CSF outflow (Figure 1E). A ventriculo-peritoneal shunt was therefore inserted, and his mobility improved to his baseline state. He did not receive any further doses of Tominersen.

This ASO therapy has led to much excitement within the HD community, but the published clinical data are limited, with no major serious adverse events reported. Here we report for the first time on a patient in receipt of this therapy who developed a communicating hydrocephalus that we diagnosed as being secondary to a sterile meningitis induced by Tominersen. This resulted in significant disability, which benefited from shunting.

Clinical experience with intrathecal ASO therapy is limited, but does include the use of the intrathecal ASO treatment (Nusinersen) for spinal muscular atrophy[3,4]. Although no cases of hydrocephalus were seen in trials of this drug, during post-marketing surveillance a number of cases of aseptic meningitis and communicating hydrocephalus were observed[5]. However, this has not been reported with Tominersen to date and given that a large Phase 3 study is underway (NCT03761849), along with other similar studies[6], it is important that this potential complication is recognised.

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TBS: 3A

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Ethical compliance statement

Ethical approval for the trial in which this patient participated was granted by London- West London & GTAC Research Ethics Committee and REC reference number was 17/LO/1502, and the patient provided written consent to take part. The patient has provided signed written consent for publication of this report. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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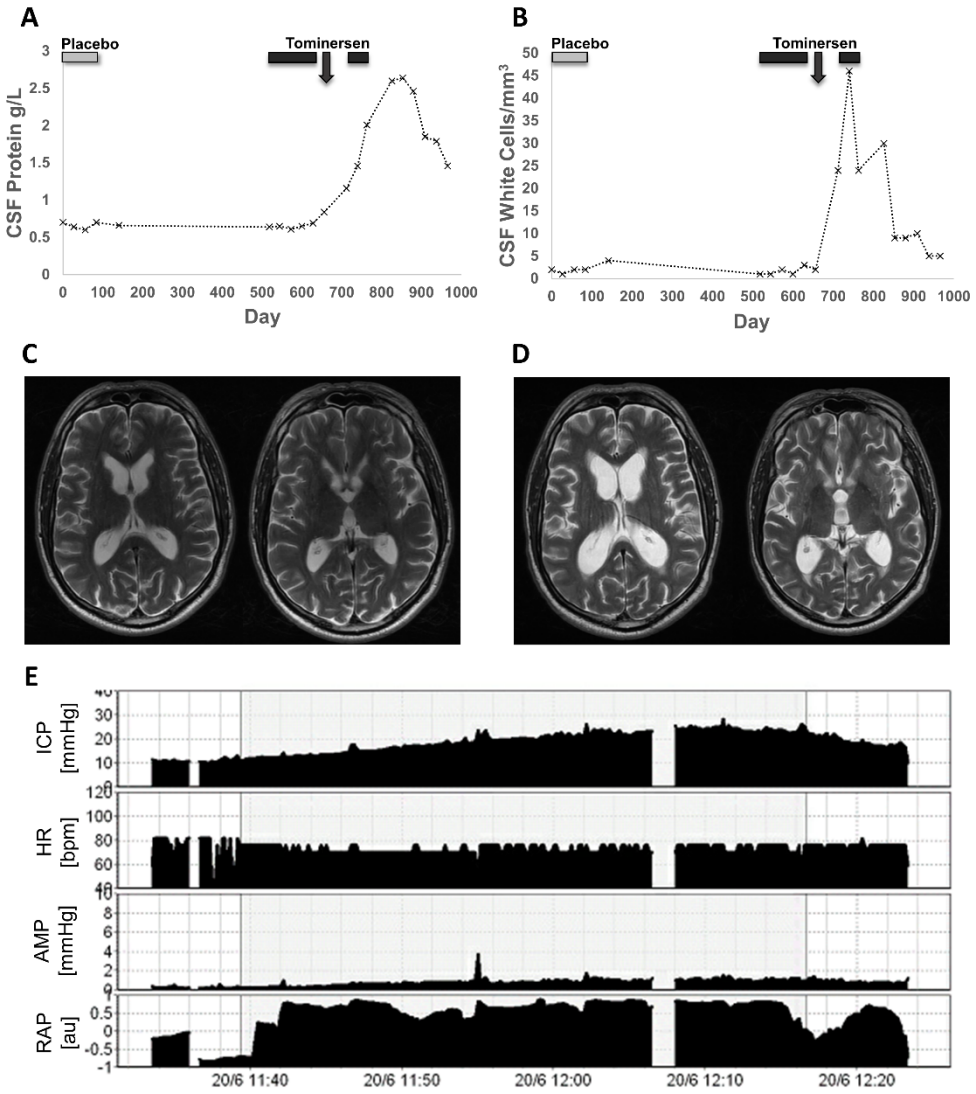

Figure 1 – Investigation results

CSF protein (A) and leukocyte count (B). Light and dark grey bars represent treatment with placebo and Tominersen respectively. Arrow indicates clinical deterioration. Axial T2-weighted MRI at baseline (C) and after deterioration (D). Lumbar infusion study (E). AMP=pulse amplitude; HR=heart rate; ICP=intracranial pressure; RAP=compensatory reserve index.