COMMENT

ENROLL-HD for MND?

Eva Pears[1,2], Louis Stokes[1,2] and Alisdair McNeill[1] ✉

European Journal of Human Genetics (2023) 31:493–494; https://doi.org/10.1038/s41431-023-01309-9

Motor Neuron Disease (MND) is an incurable neurodegenerative disorder. In around 20% of cases there is an identifiable monogenic cause, with autosomal dominant inheritance in the majority of families [1]. The most commonly identified monogenic causes are missense variants in *SOD1* and an expansion in *c9orf72*. Many contemporary treatment trials for MND utilise novel therapeutics which target specific molecular genetic causes of MND. For example, Tofersen for *SOD1*-MND in the ATLAS trial [2]. Given the rarity of monogenic MND, a major challenge for such trials is recruiting a sufficient number of participants. Based on the experience of the VALOR study for Tofersen - which demonstrated better secondary trial outcomes in those who received Tofersen earlier - it is likely that future trials may seek to recruit participants who carry causal genetic variants but who do not have overt clinical features of MND. This poses an additional challenge - since predictive genetic testing for MND in clinical practice is relatively uncommon leading to even smaller eligible cohorts [3]. What then can be done to address these barriers to clinical trials?

The ENROLL-HD study is a prospective, international, multicentre study which recruits people with expansions in the *Htt* gene causing Huntington's Disease (HD) [4]. Participants have yearly phenotyping visits where multiple assessments of cognition and motor function are made. This provides a trial ready cohort of participants, with clinical characteristics that represent the whole spectrum of HD. While MND and HD are genetically and clinically distinct, they share some common features that might indicate that a project based on ENROLL-HD could be of value in MND. For example, it is now recognised that, like in HD, genetic MND has a defined prodromal period with subtle cognitive and motor abnormalities [5]. An ENROLL-MND/ALS project could be initiated by recruiting participants who have a causal MND gene variant identified through clinical genetic testing; as is the process in the UK for identifying ENROLL-HD participants.

For such an ENROLL-MND/ALS project to work, predictive genetic testing for MND would have to be occurring in a routine healthcare setting (as it does for HD). To examine this, we undertook a service evaluation of predictive genetic testing for MND undertaken at Sheffield Children's Hospital NHS Foundation Trust for an 18 month period. We identified 46 referrals for predictive MND genetic testing (30 male), all of which had an affected first degree relative. In 38% of cases, there was no causal genetic variant known in the family. When a causal gene was known, 50% was *c9orf72*, 10% had an affected relative with a *SOD1* variant, and 2% *TBK1*. Of those in whom a causal genetic variant was known, 38% (10/26) went ahead with genetic testing and 62% (16/26) did not. The most common reason for proceeding with genetic testing was for reproductive information. This is in keeping with published reports that indicate predictive genetic testing for MND is happening with appreciable frequency in routine healthcare settings [6]. It is important to acknowledge that the numbers of people seeking predictive testing for MND may increase due to perceptions that an effective treatment is available, and this would need to be carefully addressed in pre-test counselling.

Setting up a prospective ENROLL-MND project would clearly be challenging. We, therefore, undertook a knowledge exchange project with ENROLL-HD clinical sites in the UK to understand how to establish and run such a project. Ethical approval was provided by the University of Sheffield (reference 045890). Qualitative interviews of participants involved in ENROLL-HD (Site Principal Investigators [$n = 2$], Research nurses/assistants [$n = 2$], ENROLL-HD management staff [$n = 1$]) and a focus group (Principal investigator, research nurses [$n = 2$]) were recorded and transcribed with consent. Transcripts were coded by a single researcher (LS) and thematic analysis was undertaken using NVivo.

Theme 1 - challenges of research site set up. The need for appropriately trained staff was reported as of major importance in establishing ENROLL-HD at a study site. One research nurse commented "*I've come into this with no background in people with Huntington's disease, so I didn't really know this population before taking part in this study so obviously needed training*". The need for formal training in both the study methodology ("*ENROLL does offer.. protocol training which is a mandatory induction, if you like, that everybody has to do … It's relatively broad, but not necessarily deep - so I echo HS's points about … watching someone do one and then doing one yourself under observation*") and the characteristics of HD was emphasised. While this was recognised as necessary, it was also reported to be time consuming.

Theme 2 - challenges of running ENROLL-HD. A lack of capacity to see all ENROLL-HD participants and take on additional studies (which recruit from ENROLL-HD) was recognised as a major challenge to running the study: "*we have quite a lot of patients and we've reached… saturation in that regard - so we can't really recruit new patients. That obviously has implications in that we've now got to have a waiting list and patients are being, sort of, turned away*". The volume of administrative work associated with ENROLL-HD was also seen as challenging; both in terms of the time taken per participant to complete all rating scales and the frequent written communication with the ENROLL-HD central management team. The need for monitoring and site visits by ENROLL-HD was recognised as important, but time consuming with frequent checking and returns of paperwork required.

[1]Department of Neuroscience, the University of Sheffield, 385a Glossop Road, Sheffield S10 2HQ, UK. [2]These authors contributed equally: Eva Pears, Louis Stokes.
✉email: a.mcneill@sheffield.ac.uk

Received: 19 December 2022 Revised: 19 January 2023 Accepted: 25 January 2023
Published online: 7 February 2023

Theme 3 - value of ENROLL-HD. ENROLL-HD was seen as a valuable resource to recruit eligible participants into clinical trials: "*Then we were in a position to do clinical trials and increase recruitment because now you've got a group of patients on whom you've got data, they've indicated that they're willing to participate in studies because they are part of ENROLL, and so if a drug company or sponsor says, 'we want x number of patients', usually n's of about 350 or 400, something like that, and 'we want them in the early stages of the disease' - well, you've automatically got got a database to go to*." In addition to clinical trials, ENROLL-HD was reported as also being able to provide valuable cohort data for observational studies on HD. Trying to help HD patients was the major motivator for taking on and running ENROLL-HD: "*So that's my motivation, it's finding effective treatments for our patients and our families. At the last count, we have something like 600 genotype positive people with HD in the area, and they need some form of hope otherwise, what's the point?*"

Theme 4 - process of developing ENROLL-HD. It was apparent that the ENROLL-HD study was not simply set up 'over night', participants reported how ENROLL-HD had developed from the previous Registry studies and the experience garnered through running those. A major consideration in setting up ENROLL-HD was ethical issues, in particular participant confidentiality: "*there are obviously significant sensitivities around any patient data that you're handling and entering it onto an electronic database system and distributing those data and bio samples through to the research community… So one of the things that we do for ENROLL-HD is at the point of consent, the participant is agreeing that their data are coded - and we use something called the HD ID, which is a nine digit code that's assigned*". Legal considerations about data protection and data sharing were also highlighted, with the need for specialist advice.

The ENROLL-HD project has facilitated multiple trials of novel therapeutics for HD. It seems plausible that a large cohort of genotyped and phenotyped individuals with variants in MND linked genes, at various stages of motor involvement, could have a similar effect on MND clinical trials. A next step to an ENROLL-MND study would be to engage with the MND community to ascertain the acceptability and perceived value of such a project. An ENROLL-MND project could use clinical predictive genetic testing for MND as a real world source of participants and follow similar protocols to ENROLL-HD but with MND specific assessments.

REFERENCES

1. Borg R, Farrugia Wismayer M, Bonavia K, Farrugia Wismayer A, Vella M, van Vugt JJFA, et al. Genetic analysis of ALS cases in the isolated island population of Malta. Eur J Hum Genet. 2021;29:604–14.
2. Miller TM, Cudkowicz ME, Genge A, Shaw PJ, Sobue G, Bucelli RC, et al. Trial of antisense oligonucleotide for SOD1 ALS. N Engl J Med. 2022;387:1099–110.
3. McNeill A, Amador MD, Bekker H, Clarke A, Crook A, Cummings C, et al. Predictive genetic testing for motor neuron disease: time for a guideline? Eur J Hum Genet. 2022;30:635–6.
4. Oosterloo M, Bijlsma EK, Verschuuren-Bemelmans CC, Schouten MI, de Die-Smulders C, Roos RAC. Predictive genetic testing in Huntington's disease: should a neurologist be involved? Eur J Hum Genet. 2020;28:1205–9.
5. Benatar M, Granit V, Andersen PM, Grignon AL, McHutchison C, Cosentino S, et al. Mild motor impairment as prodromal state in amyotrophic lateral sclerosis: a new diagnostic entity. Brain. 2022;145:3500–8.
6. Amador MD, Gargiulo M, Boucher C, Herson A, Staraci S, Salachas S. Why and why? Requested for presymptomatic genetic testing for Amyotrophic Lateral Sclerosis/Frontotemporal dementia vs Huntington Disease. Neurol Genet. 2021;7.

AUTHOR CONTRIBUTIONS

AM conceived and supervised the study, wrote the first draft of the manuscript. EP analysed data and edited the manuscript. LS analysed data and edited the manuscript.

FUNDING

Motor Neuron Disease Association Healthcare Project Grant (McNeill/Oct21/967-794). University of Sheffield Knowledge Exchange funding.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL

University of Sheffield (045890).

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Alisdair McNeill.