

Institution: University College London
Unit of Assessment: 4 - Psychology, Psychiatry and Neuroscience
Title of case study: Rare diseases research and translation in muscle channelopathies: establishing a national diagnostic service and developing the first proven effective treatment for patients
<p>1. Summary of the impact</p> <p>Understanding and finding treatments for rare disease represents a major challenge across medicine. We have shown this is possible for rare muscle channelopathies and our work has directly benefited the lives of patients. Our 15 year basic research programme has elucidated the genetic architecture and identified new disease mechanisms for these disabling muscle conditions. We also determined the true disease frequency through the only UK epidemiology study. We translated fundamental research into new DNA-based diagnostic testing and electrophysiological diagnostics for rapid and reliable diagnosis. Our research led directly to our centre being commissioned by the NHS (£6m) as the only UK centre for diagnosis and management and we established the UK NHS national genetics channelopathy reference laboratory. We have built the world's largest genetically stratified patient cohorts which allowed us to lead the first international randomised controlled trial. This trial showed clear efficacy of a reprofiled mexiletine. This led to a successful European orphan product status application for this indication and national treatment guidelines.</p>
<p>2. Underpinning research</p> <p>Many important neurological diseases are episodic causing patients to experience attacks of unpredictable severe neurological dysfunction separated by periods of apparent normality. The commonest episodic neurological disorders are epilepsy and migraine and their precise molecular pathophysiology is an important unsolved neuroscience challenge. In addition, there are severe disabling disorders of episodic muscle dysfunction such as episodic total muscle paralysis and intermittent and severe disabling muscle stiffness-myotonia affecting 1 in 50,000 people worldwide.</p> <p>Over the last 15 years we have established a world leading collaborative interdisciplinary clinical, genetic and cellular electrophysiological research programme led by Professor Michael Hanna in the UCL Institute of Neurology that has progressed fundamental understanding of the pathophysiology of episodic neurological diseases, and has resulted in new diagnostic tests speeding diagnosis and improving patient outcomes. We collated the world's largest cohort of over 1,800 families with inherited channelopathies and have identified hundreds of unique mutations in specific genes responsible for the diseases. The molecular electrophysiological consequences on single ion channel function have been studied using detailed cellular expression techniques allowing a more precise understanding of the underlying pathophysiology. Many key observations have been made that have resulted in improved fundamental knowledge which has translated into improved diagnostics and patient outcomes [1].</p> <p>By studying large groups of patients with different intermittent muscle symptoms we have been able to show how genetic dysfunction of muscle sodium, potassium, calcium or chloride channels can relate to specific episodic muscle conditions including periodic paralysis, muscle stiffness syndromes (myotonia) and episodic cardiac arrhythmias [2]. We have shown that the genetic architecture of the commonest form of periodic paralysis predicts the presence of an abnormal gating pore current in muscle sodium or calcium channels supporting the presence of a brand new mechanism for disease causation [3]. We have also defined previously unrecognised neonatal ion channel diseases including intermittent neonatal hypotonia and neonatal stridor. In addition, we have shown that mutations in important presynaptic neuronal potassium and calcium channels can lead to episodic ataxia – a disorder characterized by profound disabling attacks of unpredictable unsteadiness. Furthermore, we have shown that such patients are 17 times more likely to develop</p>

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epilepsy compared to the background population risk [1].

We have shown that therapy response relates to genotype and this has directed more effective therapy selection with clear positive patient impact [4]. We developed highly specialized electrophysiological techniques that we apply to patients and we have shown that this allows us to predict the likely genotype and direct genetic testing [5].

We have led international randomised controlled trials in the UCL MRC Centre for Neuromuscular Disease, Directed by Hanna, and recently established the first proven treatment in muscle channelopathy [6]. This has led to a successful European orphan status applications and new guidelines.

3. References to the research

- [1] Kullmann DM, Hanna MG. Neurological disorders caused by inherited ion-channel mutations. *Lancet Neurol*. 2002 Jul;1(3):157-66. [http://dx.doi.org/10.1016/S1474-4422\(02\)00071-6](http://dx.doi.org/10.1016/S1474-4422(02)00071-6)
- [2] Fialho D, Schorge S, Pucovska U, Davies NP, Labrum R, Haworth A, Stanley E, Sud R, Wakeling W, Davis MB, Kullmann DM, Hanna MG. Chloride channel myotonia: exon 8 hot-spot for dominant-negative interactions. *Brain*. 2007 Dec;130(Pt 12):3265-74.
- [3] Matthews E, Labrum R, Sweeney MG, Sud R, Haworth A, Chinnery PF, Meola G, Schorge S, Kullmann DM, Davis MB, Hanna MG. Voltage sensor charge loss accounts for most cases of hypokalemic periodic paralysis. *Neurology*. 2009 May 5;72(18):1544-7. <http://dx.doi.org/10.1212/01.wnl.0000342387.65477.46>
- [4] Matthews E, Hanna MG. Muscle channelopathies: does the predicted channel gating pore offer new treatment insights for hypokalaemic periodic paralysis? *J Physiol*. 2010 Jun 1;588(Pt 11):1879-86. <http://dx.doi.org/10.1113/jphysiol.2009.186627>.
- [5] Tan SV, Matthews E, Barber M, Burge JA, Rajakulendran S, Fialho D, Sud R, Haworth A, Koltzenburg M, Hanna MG. Refined exercise testing can aid DNA-based diagnosis in muscle channelopathies. *Ann Neurol*. 2011 Feb;69(2):328-40. <http://dx.doi.org/10.1002/ana.22238>.
- [6] Statland JM, Bundy BN, Wang Y, Rayan DR, Trivedi JR, Sansone VA, Salajegheh MK, Venance SL, Ciafaloni E, Matthews E, Meola G, Herbelin L, Griggs RC, Barohn RJ, Hanna MG; Consortium for Clinical Investigation of Neurologic Channelopathies. Mexiletine for symptoms and signs of myotonia in nondystrophic myotonia: a randomized controlled trial. *JAMA*. 2012 Oct 3;308(13):1357-65. <http://dx.doi.org/10.1001/jama.2012.12607>.

4. Details of the impact

Patients with genetic muscle channelopathies experience debilitating episodes of muscle paralysis (periodic paralysis) and/or episodes of severe muscle stiffness (myotonia or paramyotonia). Many patients develop significant disabling permanent muscle weakness over time. Accurate diagnosis is difficult as the conditions are rare, so affected patients often experience a long delay of years before a correct diagnosis is achieved and effective treatment instituted. Unfortunately patients are often misdiagnosed and sometimes the variable severity and intermittent nature of some of the symptoms leads to the erroneous suggestion that the symptoms are psychological. Specialist clinical, electrophysiological and molecular genetic assessment is required to make an accurate diagnosis.

As a result of our research, our centre was commissioned by NHS Highly Specialised Services to provide the only diagnostic and treatment centre in the UK for channelopathies. We are directly funded by the Department of Health to provide this service, which has received in excess of £6m to date. Our clinical service offers a one-stop, same-day assessment in which over 2,000 patients to date have been evaluated clinically and then undergo detailed electrophysiological testing in collaboration with a consultant neurophysiologist. With informed consent, patients are then offered

detailed genetic testing to achieve a DNA-based diagnosis in the DNA laboratory. Patients are followed up to receive genetic counselling and treatment. Effective medications are available in accurately diagnosed patients and often significantly improve quality of life [a]. We are now the only UK national reference laboratory for genetic muscle channelopathies, and our service is recognised by the European network for rare disease diagnosis [b].

Our research has defined the best practice in treating patients with these rare conditions, as recognised by the Specialised Commissioning Group who say: *“The work of the Queen Square NCST group collating and the related research group has been at the forefront of developing the international evidence base for best practice in diagnostics [DNA and Electrophysiology] and patient management over the past 10 years”* [c]

In terms of diagnostics, we have devised very efficient pathways including novel electrophysiological protocols to aid rapid diagnosis and gene testing selection [d]. We have performed over 8,000 genetic tests and 1,000 electrophysiological tests on patients since the service began. Previously this patient group often did not receive an accurate diagnosis or their conditions were labelled as psychogenic. Often there were unacceptably long delays in making the diagnosis and this has been changed.

As described in section 2, our highly phenotyped genetically stratified cohorts have allowed us to lead the first international randomised trial of a treatment in a muscle channelopathy. This identified an effective treatment for muscle channelopathy patients and was published in JAMA 2012 with an accompanying full editorial entitled “Mexiletine for the treatment of myotonia: a triumph for rare disease networks” [e]. It also attracted much attention from patient groups and the scientific community [f]. We now have successfully obtained exclusive Orphan drug indication for mexiletine with the European Medicines Agency which is a critical step in enabling and supporting the process for full marketing authorisation and European licensing of mexiletine for this indication [g].

We support many patient organisations and provide national patient education days. Hanna is a member of the Medical Advisory Council for Periodic Paralysis International, an international patient organisation based in Canada [h]. He also acts as scientific advisor to the Channelopathy Foundation, based in Switzerland [i]. At the Centre for Neuromuscular Diseases we hold annual Patient Information Days on muscle channelopathies; these include interactive patient talks, opportunities to meet scientists and doctors and patient-led “ask the experts” question sessions [i].

5. Sources to corroborate the impact

[a] Website of the Centre for Neuromuscular Diseases:

http://www.cnmd.ac.uk/our_services/clinical_services/Muscle/Muscle_Channelopathy

And see current service specification: <http://www.england.nhs.uk/wp-content/uploads/2013/06/d04-diagn-serv-rare-neuromusc.pdf>

Number of patients treated and tests carried out can be verified by the Executive Administrator, the Centre for Neuromuscular Diseases, National Hospital for Neurology and Neurosurgery. Contact details provided.

[b] http://www.orpha.net/consor4.01/www/cgi-bin/Clinics_Search.php?lng=EN&data_id=41570&Expert%20centres=Rare-Neuromuscular-Disorders--Muscle-Channelopathies--NHS-Specialised-Service&title=Rare-Neuromuscular-Disorders--Muscle-Channelopathies--NHS-Specialised-Service&search=

[c] See page 9-10 of the 2012 Service Specification. 14 publications from our group are referenced.

http://www.specialisedservices.nhs.uk/library/36/Service_Specification_and_Standards_Rare_Neuromuscular_Disorders_1.pdf

[d] Burge JA, Hanna MG. Novel insights into the pathomechanisms of skeletal muscle

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channelopathies. *Curr Neurol Neurosci Rep.* 2012 Feb;12(1):62-9.

<http://dx.doi.org/10.1007/s11910-011-0238-3>.

[e] Editorial in JAMA: Hoffman EP, Kaminski HJ. Mexiletine for treatment of myotonia: a trial triumph for rare disease networks. *JAMA.* 2012 Oct 3;308(13):1377-8.

<http://dx.doi.org/10.1001/jama.2012.12906>.

[f] Study welcomed by the Myotonic Dystrophy Foundation (patient group):

<http://www.myotonic.org/mexiletine-myotonia-new-use-old-heart-drug>

Discussed in NEJM Journal Watch: <http://neurology.jwatch.org/cgi/content/full/2012/1009/1>

Article on Science Daily: <http://www.sciencedaily.com/releases/2012/10/121002161757.htm>

Article from the National Center for Advancing Translational Sciences:

<http://www.ncats.nih.gov/news-and-events/features/mexiletine.html>

[g] EMA/OD/182/12:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/orphans/2013/10/human_orphan_001268.jsp&mid=WC0b01ac058001d12b

[h] <http://hkpp.org/about-us/medical-council>

[i] <http://www.channelopathy-foundation.org/mentors.html>

[j] http://www.cnmd.ac.uk/our_services/patients/patient_2