Annual Report October 2019

Rare Neuromuscular Disorders Group

Congenital Myasthenic Syndromes

Oxford University Hospitals NHS Foundation Trust

Contents

The Congenital Myasthenic Syndrome (CMS) service at The John Radcliffe Hospital combines a specialist genetic analysis laboratory with a dedicated inpatient (funded locally) and outpatient clinical service to offer a multidisciplinary service for patients across the country.

The core CMS team comprises the following professionals**:**

Clinical team

Dr Jackie Palace	Consultant Neurologist (Service Lead)
Dr Sithara Ramdas	Consultant Paediatric Neurologist
Dr Pinki Munot	Consultant Paediatric Neurologist (GOSH)
Dr Ravi Knight	Consultant Neurophysiologist
Dr Pedro M Rodriguez Cruz	CMS Clinical Fellow
Marzena Hilarowicz	CMS Service Co-Ordinator
Hayley Ramjattan	Neuromuscular Physiotherapist
Mary Quirke	Myasthenia Specialist Nurse
Rosie Everett	Specialist Nurse
Julia Goodgame	Neurological Clinical Services Manager

Laboratory team

Weatherall Institute of Molecular Medicine

Prof David Beeson	Lead Molecular Geneticist
Dr Wei-Wei Liu	Molecular Geneticist
Dr Judy Cossins	Molecular Biologist
Dr Richard Webster	Post-Doc Electrophysiologist Medical Researcher
Ms Susan Maxwell	Research Assistant

Oxford University Hospitals Team

Dr Carolyn Campbell	Director of Genetics Laboratories
Dr Tracy Lester	Principal Clinical Scientist
Dr Mike Oldridge	Clinical Scientist

Service overview

The service sees about 220 patients each year as outpatients and offers remote advice to doctors, patients and their carers around the country regarding the diagnosis and management of CMS patients. The clinical team review patients primarily in an outpatient setting, often performing additional investigations, such as QMG scores (Quantitative Myasthenia Gravis Score), pulmonary function testing (spirometry) and EMGs (Electromyogram) in addition to genetic testing.

Consultants

There are five Consultants in the service (two Paediatric Neurologists, two Neurophysiologists and one Adult Neurologist). This includes outpatient clinics, email/telephone advice, genetic reviews and inpatient reviews when necessary.

Clinical Training Fellow

The Clinical Fellow's post is split between the NHS clinical service and the University laboratory service and works as a link between both services. The Clinical Fellow provides specialised assessments in clinic (QMG scores) and gives remote advice to patients and healthcare professionals and is in charge of data collection and database maintenance.

Molecular Genetics

Professor Beeson in his role as the lead for the CMS genetics service provides valuable input into directing appropriate testing and treatment. This includes determining the disease mechanism on all newly identified mutations in known CMS-associated genes and looking for novel genetic causes of CMS where mutations are not identified in the standard CMS-associated genes.

Consultant Neurophysiologist

Dr Ravi Knight and Dr Adam Molyneux perform all neurophysiological studies in Oxford, and Dr Matthew Pitt at GOSH, which include standard EMGs, repetitive nerve stimulation and single fibre EMGs.

Neuromuscular Physiotherapist

The CMS service has a dedicated 0.2 WTE Neuromuscular Physiotherapist, who attends both the adult and paediatric clinics. The role of the Neuromuscular Physiotherapist is to support the assessment and management of patients in clinics; using standardised assessment tools, specialist physiotherapy assessment and treatment skills, and offer guidance on exercise, activity levels and participation. This support is particularly important in the adult population where access to specialist physiotherapy in the community can be patchy. The role extends to care outside of clinics, with links to community therapists, direct contact with patients, offering guidance on exercise regimes and activity pacing, and supporting coordinated medical input during hospital admissions.

Specialist Nurse

The role of the Myasthenia Nurse is wide ranging, either providing direct or remote care, or practical advice to patients, families and the MDT. In clinic they are available to provide education and support to patients and families recently diagnosed or dealing with the long term psychological, physical and practical issues of chronic illness. They are a readily accessible point of contact for patients and families via email or telephone contact, either providing advice or signposting. If patients and families are receiving input from the MDT, they are a reference point for specific condition related information to support care delivery and management to enable patients to live well. Patient education is also a large part of the role.

CMS Service Co-Ordinator

Marzena Hilarowicz, Co-ordinator oversees the administration of the service, the Patient Day, liaises regarding the CQUIN meetings, and has contact with other hospitals on a daily basis, and is a first point of contact for the patients and professionals along with the nurse. They are responsible for co-ordinating information from referring physicians prior to review by the Clinical Team, sending out service information literature and details on patient days. She is also responsible for setting up remote clinics including contracts for the staff, travel arrangements and updated genetic information. She also acts as a liason with the laboratory and multi-agency professionals who may be involved in the care locally.

Clinical Service

There are weekly Oxford based clinics which alternate between adults and paediatric athough where all ages from one family are being seen, these are arranged jointly. In addition there are twelve full-day joint clinics with the GOSH team, which alternates between Oxford and London. This allows good practice to be shared between the centres and challenging diagnoses to be discussed in a larger MDT set up.

In addition, we held a joint Paediatric clinic at St Thomas' hospital on the 13 September 2018 with Dr Heinz Jungbluth. We also held an adult joint clinic at King's College Hospital with Dr Fiona Norwood on 25 January 2019. This year we have a joint clinic at Bristol's children hospital for the first time on 8 May 2019.

We would like to expand our remote clinics to other locations in the future, such as Glasgow with Dr Maria Farrugia and contracts are already set up for Newcastle with Dr Chiara Bettolo to take place in March 2020.

Our paediatric clinics also see children with myasthenia gravis because this is the main differential diagnosis and because it is also rare and thus many paediatric neurologists have little experience of managing this condition which untreated can be life threatening.

Both the clinical and laboratory teams offer an advice service to Healthcare Professionals around the country and overseas. This involves e-mail, telephone and letter correspondence regarding numerous patients, including those seen in clinic who are under local follow-up and patients who are unable to be seen at the centre due to geographical access issues or severity of illness, and children/neonates in crucial care with possible or known CMS. Generic advise to the myasthenia charity (MYWARE) on questions they receive from patients is also given.

In 2016 we were awarded, in collaboration with the Newcastle Muscle Group, Healthcare provider status for the European Reference Network (ERN) for rare neuromuscular disorders. The European Commission (EC) is supporting Member States in the development of European Reference Networks (ERNs) to link existing highly specialised healthcare providers across Europe, such as the CMS service and other neuromuscular services in Oxford. The development of ERNs will facilitate timely access to care, both diagnosis and treatment, by centralising knowledge and experience, medical research and training, and resources for these diseases and conditions. A 3rd EURO-NMD Annual Meeting is taking place on the 6th-8th November 2019 in Ferrara, Italy, to discuss common strategies in neuromuscular disorders. Due to the current political uncertainty of "Brexit", terms and conditions of ERNs might need to be revised in the future for UK centres participating in these networks. However, the most likely scenario at present is that UK centres will continue as part of the ERN networks but do not lead them.

The CMS Service has Telemed appointments available within our clinics, where we offer phone call appointments for patients who are unable to attend clinic due to travel difficulties and not requiring direct assessment. These are rotated between face to face and telephone appointments. . In the previous year we set up a "self-assessment QMG form to allow patients to do their own assessment to allow us to monitor patients evolution remotely more accurately

The clinical and genetic research teams offer an advisory service to the diagnostic genetic laboratory on specific genes that need testing usually after a questionnaire or clinical information from the referring clinicians. This part of the service reduces the gene screening activity and keeps the costs down. These are referred to as "genetic reviews".

In addition, the University of Oxford and Muscular Dystrophy UK (MDUK) charity have recently founded the MDUK Oxford University Neuromuscular Centre in January 2019 to focus on the urgent mission of accelerating the discovery, development and deployment of new medicines to combat devastating neuromuscular diseases. The Centre builds on the already excellent research, training and patient care in Oxford to drive the development of novel experimental therapies more rapidly and increase national clinical trial capacity in neuromuscular diseases. The Centre is housed by the University of Oxford's Department of Paediatrics and spans across multiple departments including the Department of Paediatrics, the Nuffield Department of Clinical Neurosciences, the Department of Physiology, Anatomy and Genetics, the Nuffield Department of Women's &

Reproductive Health, the Department of Chemistry and the Oxford University Hospitals Neurology Services. The CMS Team are part of this collaboration and will be liaising over new outcome measures and genetic modification treatments.

Genetic service

The Diagnostic Genetics Laboratory at the Churchill Hospital, Oxford provides specialised genetic screening for patients with suspected CMS or related rare neuromuscular conditions. There are currently a number of genes screened for that are associated with CMS: *CHRNA1, CHRNB1, CHRND*, *CHRNE, CHRNG, RAPSN, COLQ, CHAT*, *DOK7, GFPT1* and *DPAGT1*. Each of these genes encodes proteins involved in maintaining the function of the neuromuscular junction.

In addition to these, further screening for *MUSK, AGRN, ALG2, ALG14, COL13A1, GMPPB, SLC5A7, LRP4, TOR1AIP1 and SLC18A3* genes is available within Professor Beeson's research group, based at the Weatherall Institute of Molecular Medicine.

If a mutation in the genetic code is identified, additional tests can also be undertaken in Professor Beeson's laboratory to determine the pathogenicity. The current functional studies available include:

- Electrophysiology to assess *AChR* channel kinetics for fast or slow channel syndromes or reduced conductance syndrome.
- *AChR* cell surface expression to test for *AChR* deficiency syndromes
- *AChR* clustering assays to test pathogenicity of *RAPSN*, *DOK7, MuSK* and *AGRN* variants
- Exon trapping to test splice site mutations and synonymous intronic variants
- Reporter assays to test for promoter variants
- Expression assays to test *CHAT*, *GFPT1*, *DPAGT1*, *MUSK*, *AGRN*, *ALG2*, *ALG14,* and *GMPPB.*

Once the screening has been performed, the patients are either reviewed in outpatient clinic, or alternatively, the details of the case are reviewed by the clinical team and remote advice offered to the referring clinician.

In addition, whole exome sequencing and whole genome sequencing are performed via Professor Beeson's group in selected cases of CMS, where the genetic cause remains unidentified and the diagnosis of CMS is undoubted. This technology helps the identification of novel variants in genes originally not CMS-related. In these cases, further studies to determine pathogenicity need to be undertaken.

As our understanding of these conditions increases, it has become apparent that treatment choice is determined by the underlying pathogenic mechanism of the CMS subtype the patient has. Some of the treatments used routinely in some CMS subtypes cause deterioration in other subtypes. Accumulated experience allowed us to develop a treatment algorithm, which is routinely used in our clinics.

Service Objectives and Outcomes

The purposes and goals of the service

- To provide easy access to our clinical services to patients in the UK
- Make a definitive CMS diagnosis (including prenatal diagnosis where requested)
- Treat effectively in collaboration with local clinicians
- Deliver high-quality health care to patients with CMS
- Provide special neuromuscular physiotherapy advice
- Provide information for patients, families and their schools and other health care professions about CMS. (See later - Page 11: Service Engagement and Communication)

Outcomes

Activity levels

The clinical team reviewed approximately 221 patients in the outpatient clinics (200 when excluding Northern Ireland, Scotland and Wales). In addition, the clinical team also reviewed the 192 patients details for the genetic lab and/or for other health care professional needing advice in the April 2018 - March 2019.

Reduced genetic reviews and gene testing activity are likely due to the easier access to exome and whole genome screening programs, and our service beginning gene panel testing. We had no inpatients.

DNA samples: the number of DNA samples received by the diagnostic laboratory was 76, compared to 137 last year. At the moment we screen a total of 11 genes by Sanger sequencing, however, in 2020 this testing will be done by exome Next Generation Sequencing (NGS) of a panel of 27 genes.

Activity Levels Recorded [Appendices]:

- Number of new and follow-up outpatient visits and geographical information. **(Appendix 3a, 3b, 3c, 3d and 3e).** The number of new referrals this year was 33 and 188 follow-up appointments.
- DNA sample activity – number of patients **(Appendix 3f),** DNA sample geographical data **(Appendix 3g).** Number of exons analysed **(Appendix 3h).**
- Day cases and inpatient activity is also reported, although this is actually outside of the Highly Specialised Funding
- Number of remote genetic reviews from April 2018 to March 2019 was 192 (steering specific genetic tests performed dependent on clinical information) **(Appendix 3i).** Number of genetic reviews per patient **(Appendix 3j)**.

- Number of remote consultations from April 2018 – March 2019 was over 240 phone calls and 250 emails. This represents our continuous effort in communication with patients and healthcare Professionals.
- Number of Telemed appointments from April 2018 to March 2019 was 13.
- Overall, activity levels in outpatients' clinics have remained stable over time in the last years but DNA samples received have reduced **(Appendix 4).**

Performance Indicators [Appendices]

- Clinic waiting times: patients are offered an appointment within *8 weeks*. This objective is met regularly and those exceeding the target is usually their own choice.
- Patient satisfaction **(Appendix 5a and see later – page 8)**
- Overall percentage of patients with definitive diagnosis of CMS **(Appendix 5b)**
- Overall percentage of patients with genetic diagnosis of CMS **(Appendix 5b)**
- Overall percentage of patients with diagnosis of CMS ruled out **(Appendix 5b)**
- Percentage of genetic reviews within 8 weeks: approximately 95-98%
- Detection rate for genetic test: the approximate detection rate in CMS for this year was approximately 17%, which is a slight increase compared to previous years. Overall, this result is similar to other rare genetic conditions.
- Turnaround time for DNA reporting: the approximate time for DNA reporting is 6 weeks per panel of genes (~6 genes). However, if the result is required as urgent, then the turnaround is 3 weeks
- Percentage of patients involved in research (enrolled in existing registries and natural history studies, biological samples donated to biobank): all patients seen in the outpatient clinic with CMS or suspected CMS are offered to take part in research studies under ethical approval (OXREC B: 04.OXB.017 and Oxfordshire REC C 09/h0606/74). The response is in general very positive with close to 100% consenting.
- The overall percentage of patients with a final diagnosis of CMS reached on new patients being referred to the CMS service was 26.60% **(Appendix 5c)**. A small percentage of patients were classified as "undefined", which means that the clinical diagnosis is unclear.
- Safety incidents, mortality and morbidity outcomes: there were no safety incidents and no CMS-related deaths.
- Quality of Life Measures.

Geographical Distribution

Geographical data of outpatient activity (**Appendix 3c, 3d and 3e**), DNA samples received (**Appendix 3g**) and remote reviews (**Appendix 3k and 3l**) are shown - We are reporting country of residence and NHS regions.

As a National Referral Centre for CMS, Oxford aims to offer equal access to patients from across the whole of England and Scotland. Some patients cite transport costs as a limiting factor. For patients living far from Oxford, we try to offer them the flexibility to schedule their appointments to fit in with leisure travel plans. In cases where the patients are physically unable to attend outpatient clinics at all, remote advice is offered to their local Clinician regarding their diagnosis and management. Otherwise we try to alternate face to face appointments with telemed appointments.

As well as offering a national service, the team also offer advice on international patients. We have a number of current collaborations with other centres regarding patients with unresolved genetics. This confirms our efforts in establishing us as a centre of international expertise in CMS. We are receiving a number of enquiries from EU countries using the S2 EU Cross-border Healthcare Directive referral process although this might change in the future due to "Brexit".

Patient satisfaction

Feedback from patients, relatives and carers offers important insight into the quality of service provided. These views are collected in the form of a questionnaire that is given to the patients and their carers when they attend an outpatient clinic appointment. We give our patients a feedback questionnaire in order to capture more information about the performance of the CMS Service measured against the quality indicators and to identify any gaps in service provision. We have been using this questionnaire since April 2013 in all our outpatient clinics. This information is collated on to our database and any negative feedback is disseminated to the CMS team for positive action and steps. 94% of our patients scored their overall experience in the CMS clinic as excellent or good despite major car parking problem, while 96% of them scored their consultation with doctors and physio as excellent or good. (**Appendix 5a**).

We receive positive comments, as well as negative feedback. The negative feedback on our questionnaires mainly relates to the parking issues that the Trust experiences.

The Trust's new parking policy came into action in April 2017 and this resulted in released extra parking for both patients and staff. The Trust is also liaising with the County Council to try and negotiate further parking places for our patients.

Some of the positive comments received this year

Everything has been positive, all Team helpful. A fantastic Team!

Everything has been amazing, our consultation was informative and I now feel relived and confident.

Always feel listened to.

Had to contact clinic outside of appointment times and the response time was excellent. Could not ask for a better service.

We are very happy to see doctors. The doctors are always helpful.

Financial update

To be presented by the OUH Financial team lead by Carol Ann Gourlay, Neurosciences Finance Manager.

Service developments

New quality-health care measures and indicators

Over the last year we developed a set of new indicators to better measure the quality of the healthcare provided by our service. These were added to our previous ones, and incorporated into our questionnaires and databases. These can be found in the service outcomes measures. In addition, we recently started to use standardised health care questionnaires (EQ-5D-5L and PedsQL) to measure the quality of life in our patients. We aim to be able to tell in the near future whether we can improve patients' quality of life in addition to their muscle strength.

We provided the following self-assessment for the three standards for Highly Specialised Services:

Alert card.

Patients are referred after first visit to the national myasthenia charity Myaware® who provides an alert card known as 'My Health Passport for Myasthenia'.

Transition

The adult clinical team works jointly with the paediatric team in the paediatric neuromuscular clinics so that both families and patients are familiarised with the whole team. In addition, clinic appointments for both adult and patients take place in the same outpatients department which minimise the impact of transition into adult services.

There is a contact phone number for all patients. Their care coordinator will be their local neurology team.

Telemed clinics and remote monitoring of patients

The Telemed clinics were set up in March 2015 as some patients were finding it difficult to attend clinic due to geographical access issues. These have been proved to be very useful for patients. The CMS Co-Ordinator liaises with the patient to arrange a telephone appointment during the CMS clinic. After the telephone consultation, a letter is dictated and sent to their doctor. We have used this method in thirteen patients so far and this has proven successful. Therefore, this is a way to

monitor patients more easily and for them to save on travel expenses, as some patients have difficulty covering the cost of travel. This also stops patients from being lost to follow-up. In addition, we have developed a simplified QMG form so that patients can do a self-assessment at home, and we can monitor their evolution even if they are not seen in clinic.

New genetic commissioning arrangements

It is not clear how the new commissioning of genetics will affect the service. We are keen for testing to only be performed in patients with clinically possible CMS because indiscriminate testing would lead to irrelevant mutations being identified requiring resource heavy functional testing.

Pilates videos for patients with neuromuscular conditions

We have collaborated with Queen's Square as part of the CQUIN group on creating Pilates videos for patients with neuromuscular conditions. The videos were already recorded and then there will be some post-production time before it is widely available. The drive came from the CMS service as we see a number of adults with CMS who benefit from modified Pilates advice. This project has been funded by one our Oxford CMS patients' fundraising.

Clinical and translational research

Newly identified CMS-associated genes and next generation sequencing

The CMS Service continues to incorporate a number of CMS patients without a current genetic diagnosis into next generation sequencing techniques. This is part of a preliminary trial into the use of next generation sequencing (as part of the Biomedical Research Centre funding) for the routine screening of genes in rare Mendelian genetic disorders. We have found mutations in a new gene not previously known to be related to CMS (*TOR1AIP1*) and further studies are currently being undertaken to elucidate the underlying physiopathological mechanisms in this subtype of CMS. Previously, using the same methodology, we were able to identify *DPAGT1*, *ALG2* and *ALG14, GMPPB,* and *COL13A1* as causative genes for CMS.

We are currently participating in the Solve-RD study - solving the unsolved rare diseases. This is a research project funded by the European Commission for five years (2018-2022) to solve large numbers of rare disease, for which a molecular cause is not known yet by sophisticated combined omics approaches, and to improve diagnostics of rare disease patients through contribution to, participation in and implementation of a "genetic knowledge web" which is based on shared knowledge about genes, genomic variants and phenotypes.

Given the number of new CMS-associated genes that are being identified Drs Michael Oldridge and Tracy Lester have developed a Next Generation Sequencing CMS panel to be used in the screening. This has been designed to detect the more common CMS variants in the genes described above. The less common CMS forms

caused by mutations in large genes such as *AGRN* and *MUSK* are currently screened for in the research laboratory.

Following the contribution of the NHS to the 100.000 genomes project and the recent creation of the NHS Genomic Medicine Service, we predict a potential restructuration of genetic services in England. However, most recent information suggest that genetic testing for common CMS genes will remain in Oxford with the creation of a CMS next generation sequencing panel.

In addition, we anticipate the likely increase in the need of interpretation of genetic variants using functional studies following the implementation of genomic medicine in England. We are currently working on development of functional assays of enzyme catalytic activity to be used to assess the pathogenic nature for variants of unknown significance for mutations in DPAGT1, GFPT1, and GMPPB. It is hoped that these can be added to our list of assays designed to give a definitive answers about pathogenicity for the increasing number of sequence variants uncovered by next generation sequencing.

Current translational research projects

As previously reported by our group, several forms of CMS show a marked beneficial response to Salbutamol or ephedrine. Recent research in our laboratory has shown that β2-adrenergic agonists have an specific positive effect in both neuromuscular junction structure and function (Clausen et al, J Neuromuscul Dis 2018) and that β2-adrenergic agonists counteract the effect of long-term pyridostigmine (Vanhaesebrouck et al, Brain 2019). We believe that these drugs provide a compensatory mechanism to stabilise the motor endplate structures, improving neuromuscular transmission. A better understanding of it will help us to provide more efficient treatments.

We are currently working in the identification of small molecules that could increase expression levels of the DOK7 protein as a novel therapeutic strategy. This has been funded partly a Myaware prize studentship from October 2016. We are also actively exploring the use of novel molecules in cell models of fast-channel CMS. We are also exploring the use of DOK7 gene therapy in different mouse models of CMS with promising preliminary results.

Future translational research projects

As stated above, an understanding of the underlying molecular mechanism of disease due to the different mutations is fed back to the clinical team to direct appropriate therapy. Next generation sequencing is revealing a series of new CMS-associated genes and projects are underway to determine how the different mutations affect signal transmission at the neuromuscular junction. Further projects are being undertaken to study the beneficial effects of salbutamol. At present the precise mechanism through which Salbutamol improves neuromuscular transmission is not known, but research into the mechanism may provide a scientific pointer to similar compounds that have greater efficacy. Ongoing collaboration with Novartis

Pharmaceuticals is helping in the development of more potent β2-adrenergic receptor agonist which, in preliminary work, has been found to be muscle-specific and therefore have markedly reduced side effects.

Service engagement and communication

Website

A webpage for the service is hosted on the OUH website and includes: patient CMS booklet, referral information and pre-referral form, as well as points of contact for Clinicians. The website has recently been updated with the contact information for the CMS Team. Patients can also access our annual reports on the website, as well as information from the Patient Day we hold, including the presentations, which patients have asked for. We endeavour to continually update the website, so the information is as up to date as possible.

Pre-attendance Clinic Information Pack

The content has been approved by the Trust Media and Communications Department. The information pack is placed on the CMS service webpage. The information pack is sent to all new patients attending the service prior to their appointment. This helps patients and families to know what to expect from their appointment. The booklet has been updated last year to include new staff members (Appendix 6).

Information in clinic

Newly diagnosed patients are given in clinic a CMS booklet, published by 'Myaware' (Appendix 7) with the latest relevant information regarding diagnosis, treatment and management of this condition. In addition, there are given a CMS-DVD with testimonies of several CMS patients, so that patients and families can understand their condition better. We also send these documents to school when requested by the parents of patients with CMS.

For patients with child bearing potential, we provide them with an information pack for Health Care Professionals regarding the safety of the most commonly used CMS drugs in pregnancy and breastfeeding **(Appendix 8)**.

Patient day

The CMS Patient Day took place on the 6^{h} April 2019 in Oxford. A total of 13 patients and their family members attended (25 in total). The agenda consisted of overviews, presentations, and breakout sessions where patients interacted with each other and the CMS team (Appendix 9). This year we had Steve Bradshaw (Myaware Benefits and Welfare Officer) who covered Disability Living Allowance (DLA), Personal Independence Payment (PIP) and general information on benefits through a breakout sessions. This year we also had a special focus on neuromuscular junctions: Dr Steven Taylor presented 3D Virtual Reality Neuromuscular Junctions

as seen before and after treatment. Also Dr Andrew Ives (Consultant in respiratory Medicine) gave a talk about respiratory support. In addition to educational objectives patients find this meeting socially and psychologically helpful because they meet with individuals who are in a similar situation as themselves and many make long-lasting contacts.

Patients completed a questionnaire feedback with a positive outcome (Appendix 10). The next National Congenital Myasthenia Patient Day is due to take place in the spring of 20209 in Oxford with a special focus on gene therapy. 'Myaware' has been informed and representatives will be attending. We uploaded the presentations onto our CMS website, via the Trusts website, so the patients can refresh themselves and other patients can have easy access to them.

CQUIN

The CQUIN requirement is designed to encourage collaborative learning and Quality Service Development is based on long standing precedent in the highly specialised services (HSS).

The meeting includes discussions of clinical outcomes, comparison of centres' outcomes, and identification of where providers need to adopt new ways of delivering consistent outcomes across all clinical teams. The meeting to discuss the 2018-2019 report will take place on 19th March 2020 in Newcastle.

Service problems

3,4-DAP supply

Although Biomarin has up to now tolerated the prescribing of the cheaper generic 3,4-DAP, in the UK we have some concerns this may change in the future. They are currently trying to obtain a licence for Firdapse in CMS in the USA and it is likely this will lead to a European licence.

Provision of Salbutamol

The problem with the manufacturing of Salbutamol modified release capsules (Ventmax®) persists. The product was discontinued in 2015 and is no longer available. There has been no replacement modified-release preparation. There are no current issues with the supply of normal formulation Salbutamol tablets or liquid formulation, which are manufactured by GSK. All our patients are doing well on the tablet or liquid formulations. However the higher costs of the salbutamol tablets compared to the previous MR version and the liquid versions has meant some GPs insisting on prescribing the liquid formulation which has a short half-life and is bulky/heavy to transport. The following information was obtained from our hospital pharmacy regarding the cost and half-life of the tablet and liquid formulations of salbutamol.

"Salbutamol s/f syrup is significantly cheaper compared to immediate release tablets (approx. 95% cheaper) but due to contract agreements and confidentiality reasons the hospital was unable to verify the precise figures. We believe the liquid is up to 100 times cheaper.

Salbutamol 2mg/4mg tablets (Activis): The manufacturer states 50% of the drug is excreted within 4 hours, and fully excreted in 24 hours. Other brands of immediate-release salbutamol tablets have been quoted to have different half lives in the range of 5 to 7.2 hours.

Salbutamol s/f syrup (Ventolin): The manufacturer does not state a half-life for its preparation. However other sources suggest is it 5 hours. For oral preparations, tablet and syrup, the bioavailability is about 50%. Here at the OUH we only keep 4mg (x28) tablets and the s/f 2mg in 5mL syrup (150mL)."

Meetings, presentations and publications

Meetings

Dr J Palace, Professor D Beeson, Dr Stephanie Robb, Dr Sithara Ramdas, Dr P Rodriquez Cruz, Dr Tracy Lester, Dr Mike Oldridge. Highly Specialised Services Clinical Outcome Collaborative Audit Workshop, Newcastle upon Tyne. 22nd June 2018.

Collaboration with Newcastle and GOSH physiotherapists on outcome measures used in clinic. Newcastle upon Tyne. Hayley Ramjattan, Dr Pedro Rodriguez Cruz. 18th January 2018.

Oral Presentations

ICNMD conference Vienna, Austria 10 July 2018

Talk: Treatment for CMS, Professor Jacqueline Palace

Neuroimmune Colloquium Berlin 11th July 2018

Talk: Congenital Myasthenia Syndromes, Professor Jacqueline Palace

Walton Centre Postgraduate Medical Education lecture 23 Jan 2019

Talk: CMS, Professor Jacqueline Palace

Paed MG Guidelines now March 2019 (Postponed from 8-10 June 2018)

Talk: CMS, Professor Jacqueline Palace

Spanish CMS Association. Talk: “Tratamiento de síndromes miasténicos congénitocs. ¿ De dónde venimos y a dónde vamos?”. Barcelona. 14th September 2019, Dr Pedro M Rodriguez Cruz

44th Oxford Muscle Symposium. Talk: “Two siblings with myasthenia and myopathy due to mutations in a nuclear envelope gene”. Oxford. 12th July 2019. Dr Pedro M Rodriguez Cruz.

British Myology Meeting September 2018- ‘ Autoimmune Myasthenia in Children- Not Just small adults’, Dr Sithara Ramdas

XV International Congress on Neuromuscular Disease, July 6 - 10, 2018 in Vienna, Austria. Workshop talk: DPAGT1, DOK7 and salbutamol. Looking for new treatment options in neuromuscular disease. Prof David Beeson

XV International Congress on Neuromuscular July 6 - 10, 2018 in Vienna, Austria. Scientific session. Synaptic stability in congenital myasthenic syndromes. Prof David Beeson.

Muscle Study Group of America, September 15th 2018. St Catherine’s College, Oxford. New molecular therapies for congenital myasthenic syndromes. Prof David Beeson.

4th International Congress on Muscle Wasting, September 23rd-27th, Ascona, Switzerland. Mechanisms and treatment with β2-adrenergic receptor agonists for disorders of neuromuscular synaptic transmission. Prof David Beeson.

Update in Neuromuscular Disorders teaching symposium. May 23rd, UCL, London. Congenital myasthenic syndromes: Genetic update and classification. Prof David Beeson.

SENA meeting. February 15th 2018. Holiday Inn, Oxford. Congenital myasthenic syndromes for the general neurologist. Prof David Beeson.

Physiotherapy Management of Congenital Myasthenic Syndrome – MDUK Care Conference, Nottingham. (June 2017) Hayley Ramjattan, NM Physiotherapist

Publications

Vanhaesebrouck AE, Webster R, Maxwell S, Rodriguez Cruz PM, Cossins J, Wickens J, Liu WW, Cetin H, Cheung J, Ramjattan H, Palace J, Beeson D β2-Adrenergic receptor agonists ameliorate the adverse effect of long-term pyridostigmine on neuromuscular junction structure.. Brain. 2019 Oct 21. pii: awz322. doi: 10.1093/brain/awz322.

Cetin H, Epstein M, Liu WW, Maxwell S, Rodriguez Cruz PM, Cossins J, Vincent A, Webster R, Biggin PC, Beeson D. Muscle acetylcholine receptor conversion into chloride conductance at positive potentials by a single mutation.Proc Natl Acad Sci U S A. 2019 Oct 15;116(42):21228-21235

Balaraju S, Töpf A, McMacken G, Kumar VP, Pechmann A, Roper H, Vengalil S, Polavarapu K, Nashi S, Mahajan NP, Barbosa IA, Deshpande C, Taylor RW, Cossins J, Beeson D, Laurie S, Kirschner J, Horvath R, McFarland R, Atchayaram N, Lochmüller H. Congenital myasthenic syndrome with mild intellectual disability caused by a recurrent SLC25A1 variant. Eur J Hum Genet. 2019 Sep 16

Vanhaesebrouck AE, Beeson D. The congenital myasthenic syndromes: expanding genetic and phenotypic spectrums and refining treatment strategies. Curr Opin Neurol. 2019 Oct;32(5):696-703

Taylor J, Craft J, Blair E, Wordsworth S, Beeson D, Chandratre S, Cossins J, Lester T, Németh AH, Ormondroyd E, Patel SY, Pagnamenta AT, Taylor JC, Thomson KL, Watkins H, Wilkie AOM, Knight JC. Implementation of a genomic medicine multi-disciplinary team approach for rare disease in the clinical setting: a prospective exome sequencing case series. Genome Med. 2019 Jul 25;11(1):46.

Takata K, Stathopoulos P, Cao M, Mané-Damas M, Fichtner ML, Benotti ES, Jacobson L, Waters P, Irani SR, Martinez-Martinez P, Beeson D, Losen M, Vincent A, Nowak RJ, O'Connor KC. Characterization of pathogenic monoclonal autoantibodies derived from muscle-specific kinase myasthenia gravis patients.JCI Insight. 2019 Jun 20;4(12).

Cetin H, Liu W, Cheung J, Cossins J, Vanhaesebrouck A, Maxwell S, Vincent A, Beeson D, Webster R. Rapsyn facilitates recovery from desensitization in fetal and adult acetylcholine receptors expressed in a muscle cell line.J Physiol. 2019 Jul;597(14):3713-3725.

Rodríguez Cruz PM, Cossins J, Estephan EP, Munell F, Selby K, Hirano M, Maroofin R, Mehrjardi MYV, Chow G, Carr A, Manzur A, Robb S, Munot P, Wei Liu W, Banka S, Fraser H, De Goede C, Zanoteli E, Conti Reed U, Sage A, Gratacos M, Macaya A, Dusl M, Senderek J, Töpf A, Hofer M, Knight R, Ramdas S, Jayawant S, Lochmüller H, Palace J, Beeson D. The clinical spectrum of the congenital myasthenic syndrome resulting from COL13A1 mutations. Brain. 2019 Jun 1;142(6):1547-1560

Thompson R, Abicht A, Beeson D, Engel AG, Eymard B, Maxime E, Lochmüller H. A nomenclature and classification for the congenital myasthenic syndromes: preparing for FAIR data in the genomic era. Orphanet J Rare Dis. 2018 Nov 26;13(1):211. doi: 10.1186/s13023-018-0955-7.

Dong YY, Wang H, Pike ACW, Cochrane SA, Hamedzadeh S, Wyszyński FJ, Bushell SR, Royer SF, Widdick DA, Sajid A, Boshoff HI, Park Y, Lucas R, Liu WM, Lee SS, Machida T, Minall L, Mehmood S, Belaya K, Liu WW, Chu A, Shrestha L, Mukhopadhyay SMM, Strain-Damerell C, Chalk R, Burgess-Brown NA, Bibb MJ, Barry Iii CE, Robinson CV, Beeson D, Davis BG, Carpenter EP. Structures of DPAGT1 Explain Glycosylation Disease Mechanisms and Advance TB Antibiotic Design. Cell. 2018 Nov 1;175(4):1045-1058

Rodríguez Cruz PM, Palace J, Beeson D. The Neuromuscular Junction and Wide Heterogeneity of Congenital Myasthenic Syndromes. *Int J Mol Sci. 2018 Jun 5;19(6).*