

Impact case study (REF3b)

<p>Institution: University College London</p>
<p>Unit of Assessment: 1 – Clinical Medicine</p>
<p>Title of case study: Alternatives to medication improve quality of life for children with epilepsy</p>
<p>1. Summary of the impact</p> <p>Our research on alternatives to medication in the treatment of childhood epilepsy has resulted in increasing rates of surgery with better outcomes, and a new clinical service – the national Children’s Epilepsy Surgery Service (CESS) – being commissioned in England and Wales. We have also developed an evidence base for ketogenic dietary therapy, resulting in an increase in service provision. Many more patients are benefiting from this therapy, which is now recommended in NICE guidelines. Throughout our programme of research we have engaged with charities and patient groups to disseminate the results of our research as widely as possible.</p> <p>2. Underpinning research</p> <p>Epilepsy affects 112,000 children and young people in the UK, of whom two thirds will respond to antiepileptic medication, or go into spontaneous remission. For the remaining third, however, seizures persist, and are associated with a reduced quality of life. Therefore, since 1993, research at the UCL Institute of Child Health’s Neurosciences Unit has investigated alternative approaches to medication, with a particular emphasis on the roles of surgery and dietary treatments as alternatives to antiepileptic drugs.</p> <p>Epilepsy surgery, targeted at removing the source of seizures, can lead to long-term seizure relief where medication has been unsuccessful. Our initial research evaluated newer imaging techniques in the detection of brain abnormalities in children with focal epilepsy utilising MRI, as well as relating these areas to seizure onset utilising functional imaging e.g. single photon emission computed tomography [1]. Further work in collaboration with the departments of Clinical Neurophysiology and Developmental Cognitive Neuroscience has developed functional MRI, both for determining areas of motor and language cortex in relation to the epileptic focus to be removed, as well as more recently linking electrical to structural brain abnormality for determining the source of seizures [2]. We have also performed outcome studies demonstrating the relative merits of early surgery in carefully selected populations, with at least maintained cognitive ability following surgery, suggesting a maintained developmental trajectory [3]. More recent work has demonstrated long-term improvements in cognition associated with weaning-off medication [4]. An epidemiological community-based cohort study has outlined the consequence of early onset epilepsy with uniformly poor outcomes, and has enabled the delineation of neurodevelopment in children with ongoing seizures by which the impact of intervention can be compared [5].</p> <p>For some patients, including those for whom surgery may not be an option, treatment may involve the ketogenic diet. This is a high fat diet designed to mimic the metabolic effects of starvation. Although this dietary treatment has been used in the treatment of childhood epilepsy for many years, our group undertook the first randomised controlled trial of its use in childhood epilepsy, and established its benefit equivalent to any new anti-epileptic drug with no difference between types of diet applied [6]. Collaborative work with UCL’s Department of Clinical Chemistry and Institute of Neurology is now being undertaken to determine a possible mechanism of action for its effect with plans for translation to clinical practice through clinical trials.</p> <p>3. References to the research</p> <p>[1] Hartley LM, Gordon I, Harkness W, Harding B, Neville BG, Cross JH. Correlation of SPECT with pathology and seizure outcome in children undergoing epilepsy surgery. <i>Dev Med Child Neurol.</i> 2002 Oct;44(10):676-80. http://dx.doi.org/10.1111/j.1469-8749.2002.tb00269.x</p> <p>[2] De Tiège X, Laufs H, Boyd SG, Harkness W, Allen PJ, Clark CA, Connelly A, Cross JH. EEG-</p>

Impact case study (REF3b)

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4. Details of the impact

Clinical practice and patient benefit

As a result of the **neuroimaging** work described above, we have increased the number of children who can be considered for surgery. This approach has underpinned the development of the epilepsy surgery programme at Great Ormond Street Hospital (GOSH), now one of the largest epilepsy surgery units in Europe and the largest in the UK. Numbers of patients per year have increased from 40/year in 2004 to 70/year in 2012 [a].

The benefit of this surgery to the patients is reduction if not abolition of seizures. Children are carefully evaluated to determine whether the seizures are coming from one area, and whether that area can be removed without further functional compromise. Secondary benefits that have been suggested have included optimisation of neurodevelopmental progress and behavioural improvement. We have evaluated outcome in several groups of children, and demonstrated benefit over time [b, c].

Since 2001, Cross has led the International League Against Epilepsy Task Force for Paediatric Epilepsy Surgery which has established referral guidelines for children with epilepsy for surgery [d], with recent evaluation of newer technologies and the development of an evaluation protocol [e]. The team has also contributed evidence and participated in the working groups of the Safe and Sustainable Paediatric Neurosurgical review currently being undertaken in England and Wales with the recent development of the national Children's Epilepsy Surgery Service (CESS), launched in November 2012, for which GOSH is the lead of four centres, and Professor Cross is Clinical Advisor [f]. The organisation Epilepsy Action report that: *"Professor Cross's work identifying both a shortfall in the number of operations undertaken in the UK and also the benefits of early surgery on neurodevelopmental and psychosocial outcomes has greatly assisted in the campaign to improve children's surgery in England. The outcome of our (and others) campaigning, underscored by Professor Cross's work, led to the NHS in England agreeing in 2012 to nationally commission children's epilepsy surgery [the CESS]"* [g].

Following our establishment of an evidence base for the **ketogenic diet**, our study is now widely quoted in service developments and the numbers of children who have been initiated and sustained on the diet in the UK have increased considerably. The ketogenic diet service at Great Ormond Street Hospital has been established and funded since 2008 with a clinical consultant lead, two dieticians and epilepsy nurse support, taking referrals from the North London area and linking in with other London centres [i]. A clinical network has been established amongst other centres now set up in the South East; Evelina Children's Hospital, St Georges Hospital and

Impact case study (REF3b)

Addenbrookes Hospital. A recent EME NIHR grant has been achieved involving nine centres across the UK for a randomised controlled trial of diet utilisation for the treatment of epilepsy in children under two years of age, led by Cross and GOSH.

Cross has worked for many years with a parent support group, Matthew's Friends, which was launched by a parent involved in our ketogenic diet study in 2004. The CEO of this organisation reports that: *"We have seen a huge increase in ketogenic services throughout the UK and globally and the trial results proved to be a major part of successful business cases being made for centres to set up a service. Without this evidence proving the efficacy of the treatment then I very much doubt we would have as many people using the diet as there are currently. Professionals from all over the world quote the results from this trial and have publically thanked the team for carrying out such a trial as the information from it has furthered their own services and allowed them to treat more patients in their own healthcare systems"* [j].

Cross is Chair of the Medical Board of the charity and works with them to support parents and professionals considering and implementing the ketogenic diet. She has been involved in several parent and professional information days, as well as preparation of material to help implementation of the diet. She was on the scientific committee of two of the three global conferences on dietary therapy of epilepsy and neurological disorders (co-organised with Matthews Friends in Edinburgh in 2010) and is leading on organisation of the meeting to be held in 2014. All have resulted in publications as supplements to peer-reviewed journals, one of which Cross co-edited in 2012 [k]. From expertise and experience gleaned from the research, she has recently jointly edited a guide and cookery book for utilisation by parents with colleagues from Australia [l].

In 2012, NICE guidelines on the diagnosis and management of the epilepsies in adults and children in primary and secondary care (for which Cross was on the Guideline Development Group) made the following recommendation: *"Refer children and young people with epilepsy whose seizures have not responded to appropriate AEDs to a tertiary paediatric epilepsy specialist for consideration of the use of a ketogenic diet."* The guideline made specific reference to the underpinning research described above as supporting evidence for this recommendation [m]. Cross was also integral to the international consensus guidelines for optimal management of children utilising the ketogenic diet, published in 2009 [n].

Media and public engagement

As a result of this work, we have contributed to various newspaper and television news articles and supplements including the Daily Mail, Daily Express, Sunday Times, Times and BBC. The epilepsy surgery and ketogenic diet programmes have also been the focus of TV documentaries and news features, the most recent at the launch of the CESS programme in 2012. Following development of the CESS, Cross has worked with Epilepsy Action on information documents about the CESS programme for parents and professionals, and the results of research performed have ensured accuracy of information [g]. She has also worked with Young Epilepsy, a charitable organisation working towards improving the lives of children and young people with epilepsy [o]. Young Epilepsy through their information and education unit, with advice from Cross, run training days for both parents and professionals, disseminating information about the benefits of surgery and early referral.

Training

In addition to the training above, the unit has developed an international reputation for training clinical fellows from around the world. Great Ormond Street is the lead for the development of the National Epilepsy Surgery Programme. Cross has been integral to the development of standardised epilepsy training courses through the British Paediatric Neurology Association. Over 3,000 paediatricians have now passed through the courses and Cross remains Chair of the Steering Committee [p].

5. Sources to corroborate the impact

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- [f] www.specialisedservices.nhs.uk/safe_sustainable/childrens-neurosurgical-services Impacts can be corroborated by Chair of the Epilepsy National Clinical Coordinating Group. Contact details provided.
- [g] <http://www.epilepsy.org.uk/info/treatment/epilepsy-surgery/children> Corroborating statement provided by Deputy Chief Executive, Epilepsy Action. Also explains Cross's work as co-clinical lead and work to develop NHS England-approved referral guidelines and patient guidelines, and public awareness work. Copy available on request and contact details provided.
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- [i] <http://www.gosh.nhs.uk/health-professionals/clinical-guidelines/the-ketogenic-diet-in-the-management-of-epilepsy/>
- [j] Supporting statement from CEO, Matthew's Friends (<http://www.matthewsfriends.org>). Copy available on request and contact details provided.
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- [n] Kossoff EH, Zupec-Kania BA, Amark PE, Ballaban-Gil KR, Christina Bergqvist AG, Blackford R, Buchhalter JR, Caraballo RH, Cross JH et al; Charlie Foundation, Practice Committee of the Child Neurology Society; Practice Committee of the Child Neurology Society; International Ketogenic Diet Study Group. **Optimal clinical management of children receiving the ketogenic diet: recommendations of the International Ketogenic Diet Study Group**. *Epilepsia*. 2009 Feb;50(2):304-17. <http://dx.doi.org/10.1111/j.1528-1167.2008.01765.x>
- [o] <http://www.youngepilepsy.org.uk> Impact can be corroborated by the CEO of Young Epilepsy.
- [p] <http://www.bpna.org.uk/pet/>