

The first two years of the UK National Barth Syndrome Service: Triumphs and Tribulations

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&

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NHS Specialised Services (NSS) Barth Syndrome Service

- Grew from an idea first proposed by Michaela Damin, after a discussion with Dr Edmund Jessop
- Dr Jessop is Chair of an advisory group to the National Commissioning Group (NCG) of NHS England
- NCG became NHS Specialised Services (NSS) in 2011
- NSS plans, funds and monitors a set of highly specialised services - surgical interventions, medical or psychiatric care, or diagnostic procedures - in England, with cover by agreement for patients living in Wales, Scotland and Northern Ireland

Alstrom syndrome	
Amyloidosis	
Bladder exstrophy	
Bridge to heart transplant (adults)	
Bridge to heart transplant (children)	
Choriocarcinoma	
Complex tracheal	
Craniofacial	Mental health service for Deaf children and adolescents (outpatient)
Epidermolysis bullosa	Ocular oncology
Extra corporeal membrane oxygenation (adults)	Ophthalmic pathology
Extra corporeal membrane oxygenation (neonates, infants, children)	Osteo odonto kerato prosthesis
Heart and lung transplant (adults)	Pancreas transplant
Heart and lung transplant (children)	Persistent hyperinsulinaemic hypoglycaemia of infancy
Islet cell transplant (cell separation and implantation)	Primary ciliary dyskinesia
Islet cell transplant (implantation only)	Primary malignant bone tumours
Liver transplant (adults)	Proton beam therapy
Liver transplant (children)	Pseudomyxoma peritonei
Lysosomal storage disorders (adults)	Pulmonary hypertension (children)
Lysosomal storage disorders (children)	Pulmonary thromboendarterectomy
Mental health service for Deaf children and adolescents (inpatient)	Rare mitochondrial disorders
	Rare neuromuscular disease
	Reconstructive surgery for adolescents with congenital malformation of the female genital tract
	Retinoblastoma
	Secure forensic mental health for young people
	Severe combined immunodeficiency and related disorders
	Severe intestinal failure
	Severe obsessive compulsive disorder and body dysmorphic disorder
	Small bowel transplant (adults)
	Small bowel transplant (children)
	Specialist paediatric liver
	Stem cell transplant for juvenile idiopathic arthritis
	Vein of Galen malformation

NCG Application

- First outline application: December 2008
- Full application: April 2009
- Scalable funding over 5 years depending on number of families diagnosed (£0.5-1.3m per annum)
- Notification of NCG approval in Jan 2010; funding commenced in April 2010
- To be run in close conjunction with Barth Syndrome Trust (BST)

Aims of Service

- **Improving Diagnosis**

- Central funding for prospective & retrospective MLCL/CL testing in boys with DCM, LVNC, fetal hydrops/cardiomyopathy, recurrent male fetal loss, idiopathic neutropenia or myopathy, etc
- Cascade testing within families once index case identified
- Antenatal diagnostics
 - Fetal sexing by two blood tests at 6-10 weeks
 - DNA testing of male fetal material obtained by CVS or amniocentesis

Aims of Service

- **Expert Assessment & Advice**

- Offer of consultation with either Drs. Steward or Tsai-Goodman within 48 hours of diagnosis
- Early introduction to CNS, dietician, genetics colleagues, etc
- Close liaison with local and regional teams in pediatrics, cardiology, hematology, etc
- Provision of detailed protocols, e.g. management of hypoglycemia, neutropenia, antibiotic prophylaxis

Aims of Service

- **Six monthly clinics**

- Continued provision of a “one-stop” clinic for children and adults with transitional care
- Serving patients from the UK and Europe
- Access on an as-required basis to a range of Consultants in cardiology, hematology, genetics, neurology, gastroenterology, metabolic and endocrinology
- More detailed cardiac investigation (echo, 12 lead ECG, 24 hour ECG, exercise testing?, MRI?)

Aims of Service

● G-CSF Provision

- Available immediately when required to all those who need it
- Mostly given on a thrice weekly basis at 2-3mcg/kg
- Delivered to home in bulk every 3 months
- Form of G-CSF which can be stored at room temperature (Lenograstim, Granocyte, Chugai Pharma)
- Training in injection and fingerprick blood testing technique by a nurse from the Homecare company
- Further support by Barth CNS and Psychologist

Aims of Service: Ongoing support

- **Clinical Nurse Specialist (CNS, half time)**
 - Visits to families & schools
 - Oversight of multidisciplinary care pathway
 - General advice/liaison, service monitoring, QM
 - Developing hand held records and Emergency Care Plans
- **Specialised dietitian (2 days/week)**
 - Analysis of food diaries
 - Advice regarding feeding problems, NG/PEG feeding
 - Protocol development

Aims of Service: Ongoing support

- **Clinical Psychologist (1 day/week)**
 - Needle phobias
 - Coping with chronic disease
 - Bereavement counselling
- **Genetic Counsellor (1 day/week)**
 - New family support, co-ordinating cascade and antenatal testing
- **Physiotherapy, occupational therapy, speech & language, social work input**

Appointing Staff

- Tricky in some respects
- All involved only part time working

The A Team



UK Situation July 2010

- Many pediatricians had never heard of Barth Syndrome
- Boys with DCM who were not neutropenic were never investigated for Barth syndrome
- DCM + neutropenia often convinced doctors of a viral aetiology, especially if they found a virus; normalisation of echocardiograms with age tended to confirm this belief
- 3-methylglutaconic (3-MGC) acid levels were relatively subtly elevated and had proven easy to miss
- Almost no doctor knew of the existence of the MLCL/CL test
- No validated test was available in a UK hospital laboratory

What were we doing in July 2010?

- Had appointed most of the main personnel, esp CNS, dietician, psychologist, genetic counsellor & administrator, and were in the process of training them
- Were developing supportive processes, e.g. leaflets, website, protocols, clinic format
- Foresaw a massive challenge in educating doctors & the general public

Who should be referred for testing?

Any male infant, child or adult presenting with one or more of the following:

- Cardiac abnormality (dilated cardiomyopathy, left ventricular non-compaction cardiomyopathy)
- Unexplained intermittent, persistent or cyclical neutropaenia
- Unexplained hypoglycaemia and/or lactic acidosis
- Proximal myopathy
- Feeding difficulties and Failure to Thrive

Any female adult with a history of multiple stillbirths, foetal hydrops or foetal cardiomyopathy.



Please contact us for further details if you are

- a parent of a child with Barth syndrome or
- a doctor who would like to arrange a test for Barth syndrome or
- treating a patient who is eligible for referral to this service

Our address

Departments of Paediatric Haematology and/or Cardiology
Bristol Royal Hospital for Children
Paul O'Gorman Building
Upper Maudlin Street
Bristol
BS2 8BJ
barthsyndromeservice@uhbristol.nhs.uk

Useful contacts:

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These consultants can all be contacted at:
Bristol Royal Hospital for Children, Upper Maudlin Street,
Bristol BS2 8BJ

The Barth Syndrome Trust (UK and Europe)

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International Registry and DNA Bank Advisory Committee
www.peds.ufl.edu/barthsyndromeregistry

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Michael Schlame, MD, New York University School of Medicine
Colin G. Steward, FRCP, FRCPCH, PhD, Bristol Royal Hospital for Children
Matthew J. Toth, PhD, Barth Syndrome Foundation Science Director



University Hospitals Bristol **NHS**

NHS Foundation Trust

Bristol Royal Hospital for Children a national centre of expertise for Barth syndrome

Barth syndrome is a rarely diagnosed genetic disorder that primarily affects males. It is caused by a recessive X-linked defect in the tafazzin gene, resulting in an inborn error of metabolism.

The main symptoms of Barth syndrome include:

- **Cardiomyopathy**
dilated and/or left ventricular non-compaction and/or endocardial fibroelastosis
- **Neutropaenia**
chronic, cyclical or intermittent
BUT some males are never neutropaenic
- **Delayed motor development, myopathy and excessive fatigue**
- **Growth delay**
that can be substantial until late teens



There is great variability between different patients and in any single individual over time. Cardiomyopathy and/or neutropaenia may not always be present at diagnosis and may vary with age.

Major clinical problems

- Congestive heart failure
- Risk of serious bacterial infections
- Motor delay and proximal myopathy
- Growth delay until late teenage years
- Exercise intolerance, lack of stamina
- Risk of fatal arrhythmia
- Hypoglycaemia and lactic acidosis

Other clinical features

- Male foetal hydrops or stillbirth
- Feeding problems and savoury food fads
- Episodic diarrhoea
- Recurrent mouth ulcers
- Characteristic facial appearance (large ears, deep set eyes), nasal quality to speech, waddling gait, positive Gower's sign
- Osteoporosis
- Chronic headache and body aches



Boys with Barth syndrome often look deceptively healthy

Please consider this disease in any boy with cardiomyopathy of any form, muscle weakness, neutropaenia or hypoglycaemia, or in any family with a history of multiple male death in childhood.

Dr C. Steward, Paediatrician, Bristol Royal Hospital for Children

The NCG Barth Syndrome Service

New Nationally Commissioned Barth Syndrome Service from 1 April 2010

Important information for all patients and doctors

Working alongside local physicians, this is a national, multidisciplinary, patient-centred service run by a team who are experts in the condition. The service includes:

- Diagnosis — biochemical cardiolipin assay. (MLCL/CL ratio), confirmed by genetic testing where indicated
MLCL/CL ratio is the only reliable diagnostic biochemical test
- Initial patient assessment and advice within 2 weeks of diagnosis
- A dedicated Clinical Nurse Specialist
- "One Stop" Clinic annually. The next Clinic will be held on 24-25th September 2010
- Close liaison with local physicians
- Retrospective analysis from Guthrie spots, stored DNA or cell lines for families with suspicious histories of male cardiac death, or families with histories of recurrent male foetal loss
- Referrals from EU countries provided that E112 is completed



The service will include expert assessment in the following areas:

Cardiology – detailed assessment of cardiac function including echocardiography, 12 lead ECG and 24-hour ECG, exercise testing etc

Haematology – assessment of possible neutropaenia, antibiotic prophylaxis, prescription of granulocyte colony stimulating factor (G-CSF), organisation of parental training on injection technique and home supply of the drug

Genetics – initial genetic counselling, antenatal testing (peripheral blood sample testing to determine sex of foetus, CVS, amnio etc)

Dietetics and metabolic issues – analysis of food diaries, advice regarding feeding problems, appropriate diets, anticipated growth rates, nasogastric and gastrostomy care, dietary adjustments to potentially alleviate symptoms

Gastroenterology – management of diarrhoea

Endocrinology – investigation into and management of delayed growth in childhood and accelerated growth after puberty

Physiotherapy and occupational therapy – assessment of muscle strength, exercise regimes to improve core stability and strength, orthotics

Psychology and Social Worker – to provide assessment and assistance in all related areas

Clinical Nurse Specialist – to ensure effective communication between all parties involved and to provide holistic and patient centred care of the highest standard. The CNS will visit affected families at home and school and will provide information and training in all matters pertaining to the proper management of Barth syndrome

Posters for Cardiologists

Could he have Barth Syndrome?



BARTH SYNDROME is an under-recognised cause of cardiac problems in boys, causing 7% of dilated cardiomyopathy (DCM) in a large American study.

An NCG Commissioned Specialised Service at Bristol Royal Hospital for Children commenced April 2010. Biochemical and genetic testing performed in Bristol at no charge to users. Retrospective diagnosis should be considered in all cases of male DCM, even if this has completely resolved.

Diagnosis: elevated ratio of MLCL/CL (monolysocardiolipin / cardiolipin) on a 3ml EDTA blood sample, or blood filter paper spots, stored Guthrie spots, fibroblasts or tissue.

Barth Syndrome should be excluded in patients with any of the following cardiac features:

- **DILATED CARDIOMYOPATHY +/- ENDOCARDIAL FIBROELASTOSIS**
- **LEFT VENTRICULAR NON-COMPACTION**

In all **NEONATAL** or **INFANT** cases plus older boys with one or more of the following:

- **SUSPICIOUS FAMILY HISTORY:** Fetal cardiomyopathy, third trimester loss, stillbirth, family history of child male death (sudden / infective / cardiac)
- **MOTOR PROBLEMS:** delayed motor milestones, proximal myopathy, fatigue
- **CHARACTERISTIC FACIAL APPEARANCE:** deep set eyes, prominent ears
- **HYPOGLYCAEMIA / LACTIC ACIDOSIS** especially in the neonatal period or infancy
- **GROWTH RETARDATION** during childhood; rapid growth in late adolescence
- **NEUTROPAENIA:** mild to severe; intermittent, cyclical or persistent
- **GUT PROBLEMS:** Feeding problems, vomiting, recurrent diarrhoea, savoury food fads
- **ABNORMAL MITOCHONDRIA** or respiratory chain tests
- **UNEXPLAINED VENTRICULAR ARRHYTHMIA** or **SUDDEN DEATH**

Further advice about free testing and the service are available at:

barthsyndromeservice@UHBristol.nhs.uk or www.barthysyndrome.org.uk

Or by telephone from Debbie Riddiford, Barth Service CNS, on 07795 507294 or Susan Western, Service Administrator, on 07767 310452

Pathologists & Geneticists

National Barth Syndrome Service



Barth Syndrome is X-linked and under-diagnosed.
Please consider in males with any of the following features:

CARDIAC: dilated cardiomyopathy +/- endocardial fibroelastosis (EFE), left ventricular compaction (LVNC), fetal cardiomyopathy, second & third trimester loss, stillbirth, ventricular arrhythmia, family history of fetal & child male death

MYOPATHY: Proximal myopathy, delayed milestones, feeding problems, diarrhoea

UNEXPLAINED "mitochondrial" disease; neonatal/infantile hypoglycaemia and lactic acidosis, abnormal respiratory chain function tests or mitochondrial appearance, 3-methylglutaconic aciduria

DYSMORPHIC FEATURES : deep set eyes, prominent ears, growth retardation during childhood, delayed bone age, rapid growth in late adolescence

NEUTROPAENIA: highly variable within & between patients; mild to severe; intermittent, cyclical or persistent but may be completely absent.
MANY SERIOUS OR FATAL BACTERIAL INFECTIONS REPORTED.

An NHS Specialised Service for Barth Syndrome commenced April 2010 at Bristol Royal Hospital for Children. Biochemical (cardiolipin analysis) and genetic (TAZ gene) testing is performed in Bristol free of charge to users. Retrospective diagnosis is recommended in all cases of idiopathic male DCM.

Diagnosis: Cardiolipin profiling is best performed on a 3ml EDTA blood sample. However, blood filter paper spots, such as stored Guthrie spots OR stored fibroblasts and many other tissues can be tested.

Further advice about free testing and the service are available at:

www.barthsyndromeservice.nhs.uk or www.barthsyndrome.org.uk

for further information please contact:

Dr Colin Steward, Service Lead, Bristol on 0117 3428044
or Debbie Riddiford, Nurse Specialist on 07795 507294
or for lab enquiries Dr Maggie Williams on 0117 3236026

National Barth Syndrome Service



An NHS Specialised Service for Barth Syndrome commenced April 2010 at Bristol Royal Hospital for Children. Biochemical and genetic testing performed in Bristol at no charge to users. Retrospective diagnosis should be considered in all cases of male DCM, even if this has completely resolved.

Diagnosis: elevated ratio of MLCL/CL (monolysocardiolipin / cardiolipin) on a 3ml EDTA blood sample, or blood filter paper spots, stored Guthrie spots, fibroblasts or tissue.

Consider Barth Syndrome in patients with any of the following features:

FAMILY HISTORY: unexplained fetal cardiomyopathy, third trimester loss, stillbirth, family history of child male death (sudden / infective / cardiac)

- **CARDIAC** dilated cardiomyopathy +/- endocardial fibroelastosis, left ventricular compaction
- **MOTOR PROBLEMS:** delayed motor milestones, proximal myopathy, fatigue
- **DYSMORPHIC FEATURES :** deep set eyes, prominent ears, tall forehead
- **HYPOGLYCAEMIA / LACTIC ACIDOSIS** especially in the neonatal period or infancy
- **GROWTH RETARDATION** during childhood; rapid growth in late adolescence
- **NEUTROPAENIA:** mild to severe; intermittent, cyclical or persistent; may be absent
- **GUT PROBLEMS:** Feeding problems, vomiting, recurrent diarrhoea, savoury food fads
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Boys at **Barth Syndrome** Clinic From April 1, 2010 NHS Specialised **Services** is funding a year round **service** for patients from throughout the UK. This involves ...

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For GENETICS teams. **Barth** ...

**And how have we done
since?**

Clinics

- Annual multi-disciplinary clinics have continued to concentrate heavily on group discussion and a social component
- Therefore run on Thursday pm and Friday so that they can run over into weekend social events

Martial Arts !



Clinic Planning

- A nightmare, for Debbie, Ness, Sue x 2 etc
- Complex, due to the number of people available to see patients, parents & siblings

Clinic Planning

- Planning is prone to last minute changes
- Now tend to survey families before clinic as to who they need/want to see
- Forcing us to reduce numbers per clinic - likely to go to three times yearly clinics soon - but that can impact the social component
- Ness and our youth worker at BRHC have introduced group sessions for the boys and siblings

Distant Patients

- System relying on S2 (previously E112) forms within EU has been difficult
- Private insurance is another complication
- Transporting patients from distant areas is challenging and unpredictable due to costs, intercurrent ill health, fatigue etc

Distant Patients

- Even proven difficult to get patients from far flung regions of the British Isles
- We have stopped encouraging EU referrals
- ...and see virtual medicine as the way forward, but funding streams remain unclear

Clinic Planning

- Transitional care has also been difficult
- As has medication control; liaison with general practitioners and colleagues in other medical teams nationwide
- This problem is bilateral.....

Customer Satisfaction

- Clinic design has relied hugely on close collaboration between BST, families and BSS in changing and adapting service each year
- Sometimes families come just for some “spot welding”, and to join in the social component
- Feedback has been excellent

Customer Satisfaction

- Families like the:
 - multi-dimensionality
 - friendliness of the staff
 - telephone contact available between clinics
 - information available online
 - undiminished social component
 - close liaison between BST and BSS
- But, as here, multiple consultations can be very tiring esp. after travelling long distances

G-CSF Service

- We supply G-CSF to 14 of the 23 boys under our routine care
- Home delivery and training have been a great success, as has fingerprick training
- Trying to wean local doctors off wanting to be in complete control of blood testing (venous) remains a challenge, as does getting results to families
- We have learned to be wary of “trough” ANCs as an arbiter of “correct” G-CSF dosing

Cardiology

- One died as a neonate due to complex arrhythmia
- Two boys have entered cardiac transplant programs since inception of the service
- One of these died of cerebral thrombosis after one day on a Berlin ventricular assist device
- The second is doing extremely well after spending 251 days on a Berlin heart

Cardiology

- Gathered more longitudinal data
- Made no fundamental improvement to management
- Seeing signs of wider awareness
- Developing new DNA sequencing techniques to make looking for underlying causes of DCM easier & hence sample referral more attractive

Dietary

- Body composition analysis
 - Truncal obesity and weight management
- Managing fads and progressing feeding
- Transition from tube feeding to oral feeding
- Monitoring micronutrient status
 - Identified Vitamin A deficiency in 40% of our population without apparent depletion of body stores in all but one case
- Optimise balance of diet (protein, arginine, fatty acids)
- Liaison and communication with dietitians across the UK about growth

Physiotherapy & OT Support

- Standard physio & OT assessments and telephone support
- Personal care issues, e.g. relating to bathing, toileting, dressing & mealtimes
- Provision of, or help with applications for, specific equipment, aids, etc
- Support and help with schooling, both on starting primary & transitioning to secondary education

Physiotherapy & OT Support

- Assistance with handwriting to address writing endurance and pencil/pen hold
- Addressing seating in class by looking at posture to promote concentration
- Looking at strategies to influence endurance during tasks at school
- Signposting for other appropriate local service involvement, educating professionals in the implications of BTHS

Psychology

- We have made huge inroads into needle phobias (courtesy of Jane & Ness)
- Systematically visiting families at home
- Worked very closely with BST to develop an educational brochure for schools & better resources for bereaved families
- Currently performing detailed neuropsychological assessment of those aged 6yrs or more to inform statementing processes etc
- Working to develop patient experience and patient reported outcome measures

Underdiagnosis

- An old theme

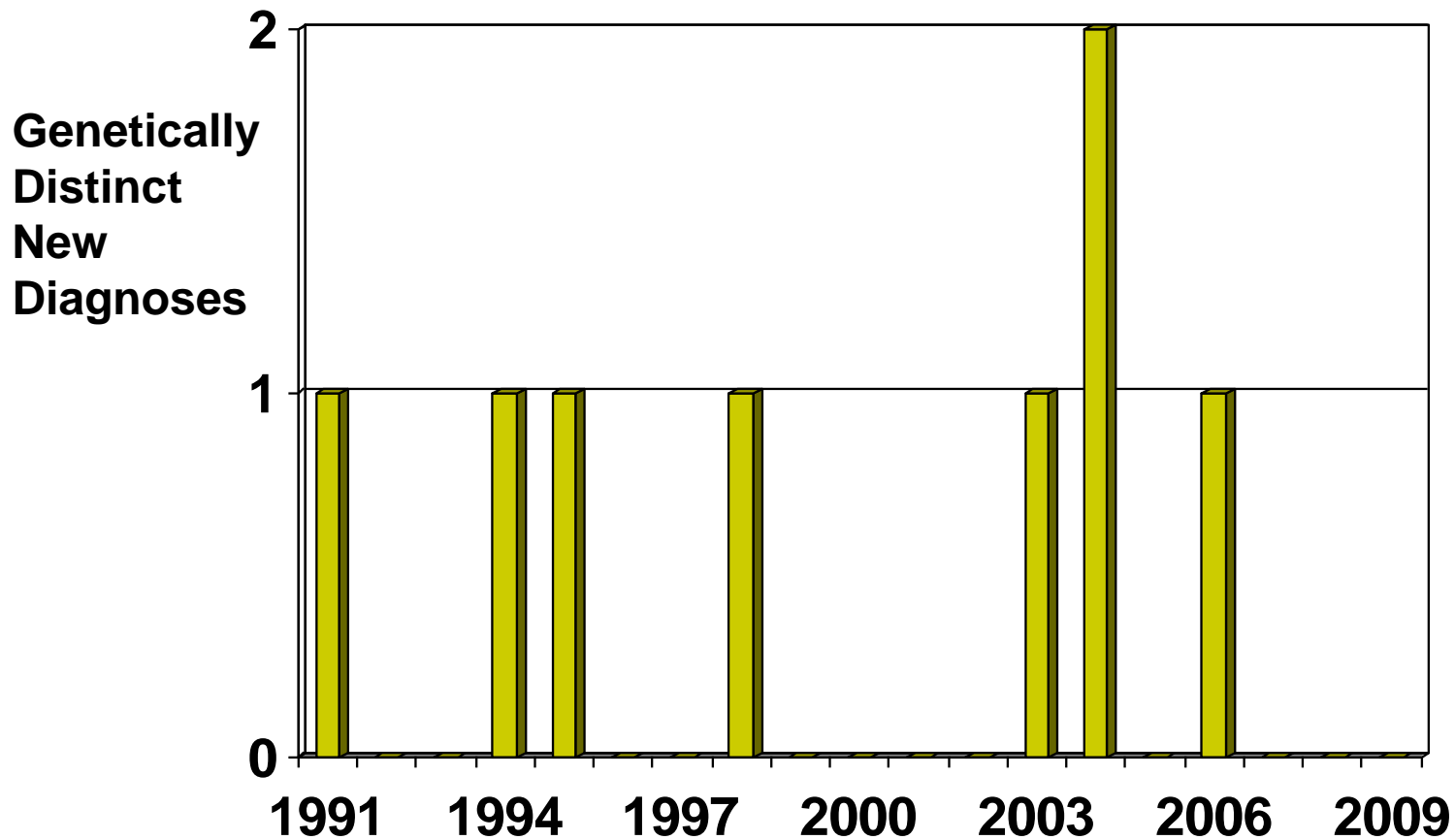
Underdiagnosis

- An old theme
- So has he not got bored with it yet?

Underdiagnosis

- An old theme
- So has he not got bored with it yet?
- NO !

Year of Presentation of Local/Regional New Barth patients to BRHC



Current Situation

- 30 unrelated UK families to date

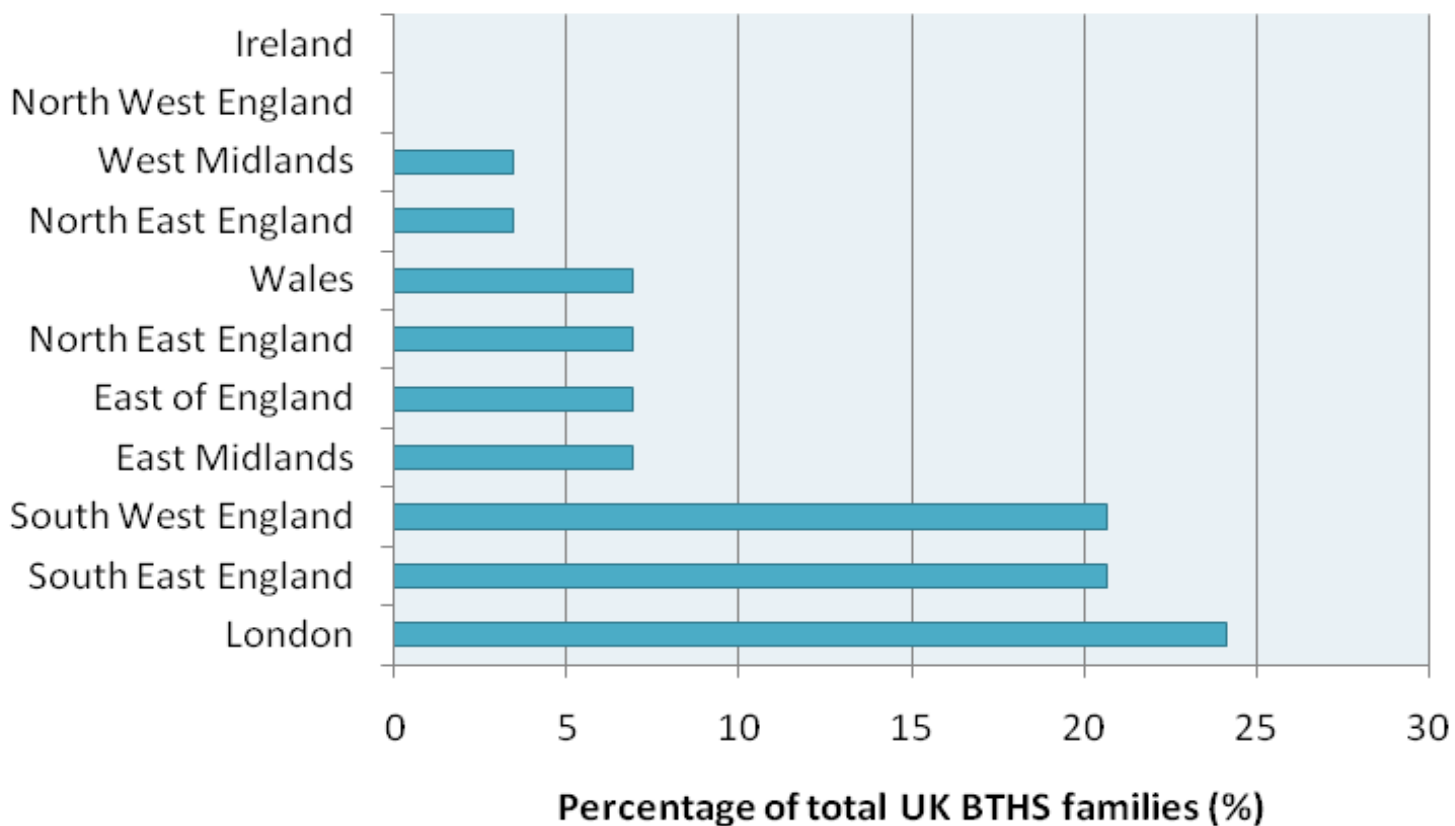
Presentations

(Bristol clinic patients with good detail available)

- 13 DCM
- 3 DCM / neutropaenia
- 2 Hypoglycaemia/Acidosis
- 1 HCM
- 1 Neutropenia
- 1 Muscle weakness
- 1 Muscle weakness / neutropenia
- 1 FTT, feeding problems

Delay to diagnosis 2 months to 3 years

Percentage of UK BTHS families by region



Barth syndrome: an X-linked cause of fetal cardiomyopathy and stillbirth

C. G. Steward^{1*}, R. A. Newbury-Ecob², R. Hastings², S. F. Smithson², B. Tsai-Goodman³, O. W. Quarrell⁴, W. Kulik⁵, R. Wanders⁵, M. Pennock⁶, M. M.⁶, J. L. Cresswell⁷, I. L. Gonzalez⁸ and P. Brennan⁹

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⁶*Bristol Genetics Laboratory, Southmead Hospital, Bristol, BS10 5NB, UK*

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Objective Barth Syndrome (BTHS) is an X-linked multisystem disorder (OMIM 302060) usually diagnosed in infancy and characterized by cardiac problems [dilated cardiomyopathy (DCM) ± endocardial fibroelastosis (EFE) ± left ventricular non-compaction (LVNC)], proximal myopathy, feeding problems, growth retardation, neutropenia, organic aciduria and variable respiratory chain abnormalities. We wished to determine whether BTHS had a significant impact on fetal and perinatal health in a large cohort of family groups originating from a defined region.

Method Case note review on 19 families originating from the UK and known to the BTHS Service of the Bristol Royal Hospital for Children.

Fetal Presentations

- 5 of 19 Families for whom we have detailed histories
 - Macerated stillborn male at 31w
Severely affected male aborted at 31w
Neonatal death shortly after birth
 - Stillborn 37w DCM/EFE
Full term; died 2 hours
Neonatal DCM: Protracted ventilation
4 other neonatal deaths & stillbirths
 - Neonatal death & stillbirth in twins
Stillbirth at 39w
 - Two third trimester miscarriages
Term stillbirth
1 stillborn twin
 - Stillbirth 33w

BTHS has claimed the lives
of 24 males in these families alone;
NO females died
as fetuses, infants or children

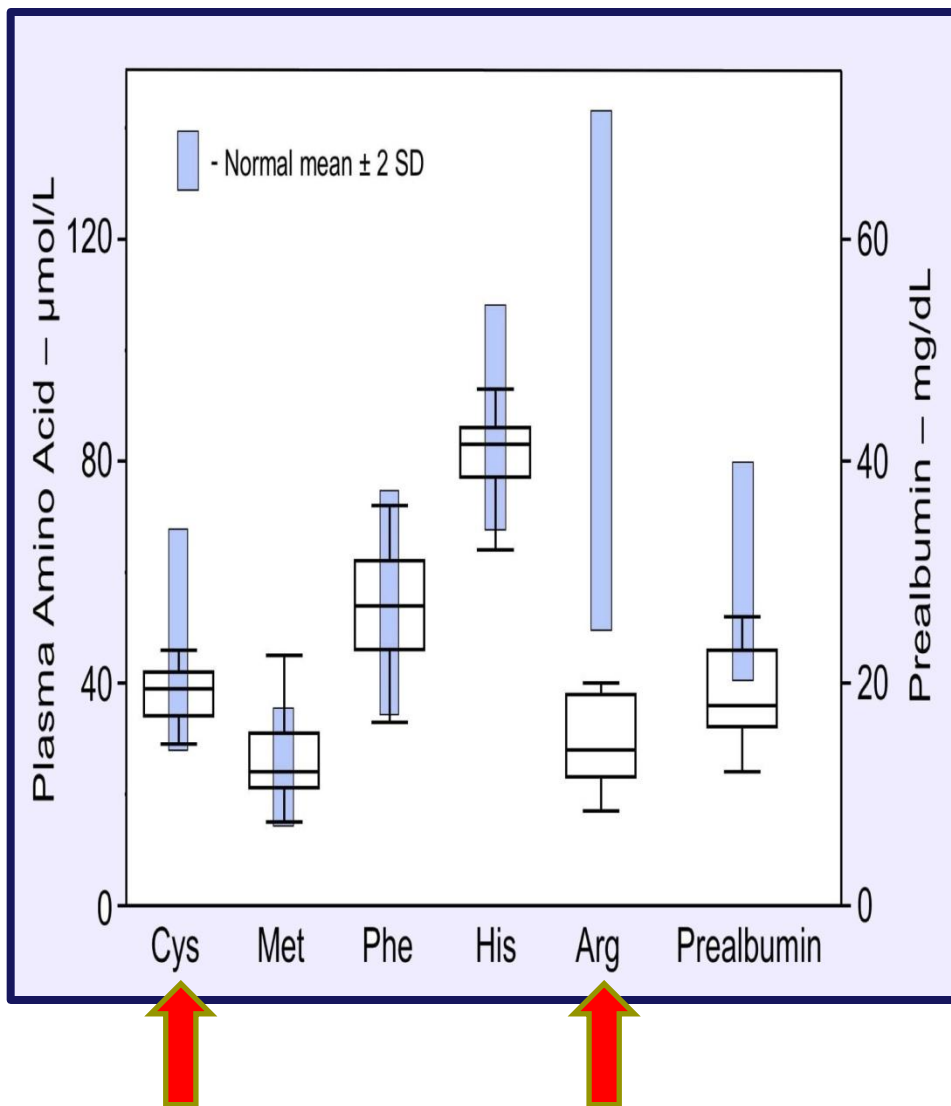
Ongoing Problems

- Getting the balance right with shared care centres throughout the UK
- Inclusion on cardiology protocols for any male with DCM
- Need for a well designed hand held record

UK General Situation June 2012 vs July 2010

- Many pediatricians has never heard of Barth Syndrome (but not for long!)
- Those who are not neutropenic are never investigated (true)
- DCM + neutropenia often convince doctors of a viral aetiology, especially if they find a virus; normalisation of echocardiograms with age confirm this belief (clearly)
- 3-methylglutaconic acid levels are only subtly elevated and easy to miss (work in progress)
- Almost none know of the existence of the MLCL/CL test (work in progress)
- No validated test is available in a UK hospital laboratory (sorted)

Richard Kelley (Kennedy Krieger Institute, Johns Hopkins) identified low arginine and cystine levels



Amino acid	UK Barth average (after 4 hr fast)	Standard Reference Range
Aspartic acid	5	1-17
Threonine	138	24-160
Serine	119	67-171
Glutamic Acid	71	1-85
Glutamine	535	37-673
Proline	293	51-271
Glycine	226	87-323
Alanine	381	136-440
Citrulline	26	10-34
Valine	198	78-326
Cysteine	15	44-96
Methionine	20	7-43
Isoleucine	51	21-89
Leucine	99	40-172
Tyrosine	68	20-108
Phenylalanine	65	25-81
Ornithine	56	22-94
Lysine	110	69-205
Histidine	76	37-125
Arginine	23	15-115

Future Plans & Aspirations

- We would like to participate in dietary trials
- We need to provide a more comprehensive diagnostic service
 - Ideally we want to test every male fetus/infant with DCM
- Development of hand held records
- We want to develop telemedicine



Special thanks to:

- The A Team
- Rob Martin, Alison Hayes & Graham Stuart
- Maggie Williams & staff of Regional Genetics Laboratory, Bristol
- Janet Stone, Charles Pennock & Helena Kemp
- Wim Kulik, Fred Vaz & Ron Wanders, Amsterdam
- The Barth Syndrome Trust



In memory of
Michael Bowen, Jr.