Research Protocol:

The UK incidence and prevalence of inherited white matter disorders

General Information

Title: The incidence and prevalence of inherited white matter disorders

Sponsor: LTHT R&I Department and Leeds Paediatric Neurology Research Fund

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Rationale and Background Information

Inherited white matter disorders (IWMDs) or leukodystrophies are diseases of the myelin due to abnormal development or degeneration.[1] These are differentiated from leukoencephalopathies that describe any disease of white matter, including acquired causes. Identification of IWMDs has greatly increased following the advances in MR-imaging which is able to identify sometimes disease-specific patterns of abnormality, however a final diagnosis is only found in approximately half of patients.[2,3,4] In those patients without a diagnosis the number and cost, both personal and financial, of further investigations whilst searching for an answer is often a huge burden to patients, families and healthcare professionals. Without specific diagnoses, outcome data and epidemiological data for individualised disorders characterisation, prognostication and potentially treatment of patients is hindered.

The worldwide estimated incidence of IWMDs is very varied, from 1:5000 to 1:50,000 live births.[5] In the last decade increased awareness and advances in neuro-genetic testing has increased the diagnosis rate in many children who in previous decades would have remained chronically undiagnosed, often undergoing multiple expensive and often invasive tests in search for an answer. Patients with inherited white matter disorders (IWMDs) or leukodystrophies would commonly have fallen within this group, often being classed as individually rare disorders, yet no robust epidemiological data is available for their incidence and prevalence within the UK. Previous studies from individual regions have suggested incidences of 100-200 patients per year, yet as some of this data stems from populations with a particularly high rate of genetic disorders it is not likely to the truly representative of the UK-wide population risk.[3]

In the UK we are developing a national inherited white matter diseases network with the aim of improving diagnosis and management for these disorders. This service may achieve recognition for national commissioning. In order to inform the development of a highly specialised national service reliable up to date epidemiological data is needed. Such data will enable service planning, identify subgroups where early access to treatments may be considered, and provide the basis for future research studies into these very rare diseases.

References

1 Kaye EM. Update on genetic disorders affecting white matter. *Paediatric Neurology.* 2001; 24(1): 11-24.

2 Schiffmann R, Van der Knaap MS. An MRI-cased approach to the diagnosis of white matter disorders. *Neurology.* 2009; 72: 750-759.

3 Bonkowsky JL, Nelson C, Kingston JL, Fillous FM, Mundorff MB, Srivastava R. The burden of inherited leukodystrophies in children. *Neurology*. 2010; 75(8): 718-725.

4 Van der Knaap MS, Breiter SN, Hart AAM, Valk J. Defining and categorising leukoencephalopathies of unknown origin: MR imaging approach. *Radiology.* 1999; 213: 121-133.

5 Heim P, Claussen M, Hoffman B, Conzelmann E, Gartner J, Harzer K, *et all.* Leukodystrophy incidence in Germany. *American journal of medical genetics.* 1997; 71(4): 475-478.

Study Goals and Objectives

The goal of our study is to determine the incidence and prevalence of IWMDs in the UK in order to inform the development of a national IWMD service.

Objectives;

1. Determine incidence and prevalence of IWMDs in the UK
2. Identify subgroups for whom early access to treatment would be useful

Study Design

Case definition: A genetic (or presumed genetic) disorder primarily affecting the white matter of the central nervous system (leukodystrophy) or a genetic (or presumed genetic) disorder where marked abnormality of white matter is demonstrable on MR imaging.

Age range for cases: Under 16 years

Inclusion criteria:

a. A new[1] (within the previous 12 months) patient with proven or suspected leukodystrophy.
b. A pre-existing patient[2] in whom a diagnosis of proven or suspected leukodystrophy has been made
c. Under 16 years (0 - 15 years, 364 days)
d. MR imaging has been performed

1. A new patient is defined as a patient that has newly presented or been newly referred to the paediatric neurology/neurodisability service.
2. A pre-existing patient is one that has been seen for review during the time of data collection

Exclusion criteria:

a. Clear evidence of an acquired leukoencephalopathy

The study would run for 13 months, with an estimated 150 cases of IWMDs in this time.

Methodology

Stage 1: Identification of cases

Cases meeting the inclusion criteria will be reported to the study team via;

a. BPNSU
b. Leeds IWMD Molecular Diagnosis Service
c. British Inherited Metabolic Disease Group Members

Stage 2a: Anonymised data collection

The reporting clinician will then be asked to provide further information including;

1. Basic demographic information (gender, age of onset, ethnicity, partial postcode)
2. Family history (consanguinuity, neurodevelopmental/neurodegenerative disorders)
3. Any precedent diagnoses (for potential exclusion)
4. Case history (brief presentation, current clinical progress and other features via targeted check-box questionnaire)
5. Other investigations (relevant serum/molecular results)
6. Diagnosis (what, when/how diagnosed, time to diagnosis)

Stage 2b: Additional data collection following consent

1. Patient details including NHS number
2. MR imaging

Stage 3: Clinical review of cases

Cases will then be reviewed centrally and classified as definite, possible or no-case.

Stage 4: Database development

Definite and possible cases will then be collected on a central database recording demographic details, selected clinical data, imaging findings and molecular and metabolic data where relevant.

Stage 5: Database analysis

At the end of the study period data on the overall incidence and prevalence of IWMDs will be defined.

Safety Considerations

The predominant safety considerations surround data management and confidentiality (see data management section).

Follow-Up

For the 1, 2 and 5 year follow up further data will be collected from the reporting clinician via questionnaire. This will include; functional status (including degree of recovery/deterioration), and confirmation of whether any diagnosis was found (if remained undiagnosed during study period).

Ethics

The predominant ethical concerns regarding this study are the issue of informed consent and data management. These issues are explored further in the IRAS/HRA application form.

Informed Consent Forms

For the first phase of the study patient/parental consent will not be required; this will include reporting of case to study team and submission of basic anonymised patient data. At this time patients and parents will be given all the study details and patient information leaflets by their

lead clinician, and permission to be contacted by the study team via telephone. If permitted the clinician will then pass their contact details back to the study team, who will follow up with a telephone consultation. If patients/parents change their minds regarding the study in the meantime, contact details will be available on the information leaflet so that they can state they no longer wish to be contacted.

Patient/parental support will then be sought by the study team (Dr L Green) via telephone consultation. Following this consent further details including patient NHS number, further clinical details and anonymised MR imaging will be collected from the local clinician.

Data Management and Statistical Analysis

Following reporting of cases data will be collected from the reporting clinician (via a REDCap questionnaire, held by Leeds Institute of Data Management). This will include; basic demographic details (gender, age at presentation, ethnicity, partial postcode), family history, case presentation (free text and targeted check-box history), and some relevant investigation results (molecular genetics etc). Following patient/parent consent we will also collect the patient NHS number and copies of patient imaging (CT/MRI). The NHS number will be used to check the patient against those reported via other methods (i.e. IWMD genetics service and the metabolic laboratories) to avoid dual reporting, but it will not be entered on the final database as at time of reporting patients will be assigned an individualised study number to include on all future forms and imaging submitted.

The NHS numbers will be stored alongside these individualised study numbers in an encrypted file saved on a secure, NHS computer. These will only be accessible by the day-to-day study coordinator Dr L Green, and the principle investigator Dr JH Livingston. All other members of the study team will only see anonymised data.

Following clinical review data for possible and definite cases will then be transferred to an anonymised study database. No additional data will be collected from that normally collected as part of healthcare provision.

Descriptive statistics will be used to summarise the key components of the database. Estimates of national incidence with confidence intervals using appropriate population estimates can then be calculated. The frequency of different symptoms will be explored in an attempt to determine possible variability within the IWMD phenotype.

Project Management

Overall project management will be performed by Dr John Livingston, the study lead, whose role will include scientific management, provision of expertise in genetic and metabolic leukodystrophy, clinical case review and case definition, data analysis.

Dr Lydia Green: day-to-day administration of the study, including response to clinical questions, data collection, management and analysis, and result write-up.

Expected Outcomes of the Study

At the end of the study period we would expect to have up to date clinical data on the incidence and prevalence of IWMDs in the UK, which would then be used to guide the development of a National IWMD service.

Secondary outcomes may also include;

1. What is the incidence/prevalence of specific sub-types of IWMD in UK and Ireland?

2. What is the distribution by age, sex and broad ethnic groupings?

3. What are the common clinical presenting features of an IWMD?

4. What proportion of reported patients have a specific diagnosis?

5. How was the diagnosis made?

6. For those with a diagnosis, what was the time between presentation and diagnosis?

7. In those without a diagnosis what further investigation was planned

8. Following MRI review were reported patients re-classified as not having an IWMD

9. How many patients were referred for consideration of entering a therapeutic trial

Dissemination of Results and Publication Policy

The results of the study will be presented to the scientific community via presentation at national and/or international meetings (British Paediatric Neurology Association and European Paediatric Society annual meetings), as well as being written up for publication. This preparation and submission process would be led by Dr Lydia Green, and supervised by Dr Livingston.

As regards informing the public we would hope to liase with regional and national patient/parent groups to disseminate information via newsletters/leaflets.

Duration of the Project

The expected duration of the project would be 13 months for case identification and data collection, followed by a further 6-12 months to complete case review, database development and statistical analysis.

Problems Anticipated

The primary issues expected are;

a. Failure to report cases to BPNSU study
   This will be addressed by regular advertisement of the study via the BPNSU website and BPNA newsletter, as well as correspondence with local neurology departments highlighting the importance of the study. Study members in a range of demographic locations will also aid in improving reporting as they each highlight cases locally.

b. Difficulties in obtaining requiring patient data (demographic, clinical, imaging and investigation results)

Budget

Funding will be provided by the Paediatric Neurology Research Fund who have committed a sum of £2000. This will be used for the BPNSU £200/year fee, stationary and postage.