NAME OF PROJECT

Retrospective Obstetric Study in Severe Congenital Protein C Deficiency

Subcommittee

Women’s Health Issues in Thrombosis and Hemostasis

Person responsible

Principal Investigator (Dr. Adrian Minford and Dr Rezan Abdul-Kadir)

SSC Chair- Dr. Maha Othman

Description Abstract

The study aims to retrospectively investigate the obstetric history of mothers who have given birth to children with severe congenital protein C deficiency (SCPCD) to determine the incidence of fetal loss during pregnancy and document the occurrence of previous neonatal death, which might be due to undiagnosed SCPCD.

Patients with severe congenital protein C deficiency (SCPCD) typically present in the neonatal period with purpura fulminans often accompanied by evidence of intracranial and retinal vessel thrombosis. The condition is autosomal recessive with both parents heterozygous often with slightly low protein C levels (normal range 65 – 135IU/dl). Severe protein C deficiency is defined as having a protein C level <1IU/dL [Goldenberg & Manco-Johnson 2008 (1)]. Occasionally patients have levels in the lower end of the moderate range (1 – 20 IU/dl.) For the purposes of this study, we will include patients with protein C levels <1IU/dl in whom acquired protein C deficiency has been excluded (both parents heterozygous, repeat low protein C levels or mutation analysis shows homozygosity or compound heterozygosity). We will also include patients with protein C levels in the range 1 – 20 IU/dl if they have a typical clinical presentation and acquired protein C deficiency has been excluded.

The estimated prevalence of SCPCD based on a carrier rate of 0.3% of the population is 2.25/million. There should be 135 cases in the UK. However, there are only 10 UK cases so far reported. Similarly, in the USA, this is fewer than 20 cases (1). This discrepancy could be due to high fetal loss of affected babies due to miscarriage or stillbirth. Another possibility is that cases of SCPCD are not being diagnosed, perhaps dying in early infancy due to presumed septicaemia or cerebral haemorrhage or rarely presenting with massive thrombosis and not being diagnosed in adulthood.

The incidence of miscarriage and stillbirth in mothers of children with SCPCD is unknown. The extent to which mothers of children with severe protein C deficiency have had previous children who succumbed to presumed septicaemia or intracranial haemorrhage in the neonatal period, which might have been due to undiagnosed SCPCD is also unknown. There is one report in the literature of 2 cases of severe protein C deficiency in which long term follow up of one of the families revealed that out of 9 pregnancies, the mother had 3 miscarriages, 1 intrauterine death at 30 weeks gestation and 1 child with
severe protein C deficiency (2). We are aware of 2 other cases, which are of possible relevance. In the case of 1 family, the mother of a patient with severe protein C deficiency had 5 miscarriages from 10 pregnancies. In the 2nd case, the mother of the affected child had a previous miscarriage at 12 weeks and a stillbirth at 37 weeks. At autopsy, the stillborn baby had an unexplained intracranial haemorrhage. The father had a history of spontaneous venous thromboembolism. The haematologist was asked for an opinion because of this background and because CNS haemorrhage had been found prenatally at 38 weeks during the current pregnancy. He suspected SCPCD, which was confirmed when the baby was born very shortly afterwards.

It would be of interest to know if mothers of children with SCPCD have a higher incidence of excessive pregnancy loss or have lost babies in the neonatal period, possibly because of undiagnosed SCPCD in the baby. If this is found to be the case, this could support the concept of trying to identify at risk couples – perhaps by targeting consanguineous couples with a history of excessive fetal loss or a history of neonatal death possibly due to undiagnosed protein C deficiency in the baby. These couples could have their protein C levels checked. Heterozygotes for protein C deficiency usually (but not always) have a slightly low protein C level.

There are beneficial implications in identifying at risk couples. Antenatal diagnosis by chorionic villus biopsy can determine if the fetus is affected if the genetic mutation is known. If so, the parents may elect for termination of pregnancy or if they do not, early elective delivery may be beneficial. It is to be noted that the incidence of blindness and neurological handicap in severe protein C deficiency is high. It is suspected that the origin of this long-term morbidity is retinal vessel and cerebral thrombosis in the fetus in the later stages of pregnancy. It is now felt that if severe protein C deficiency is diagnosed antenatally, early (32-34 weeks) elective delivery should be strongly considered to avoid blindness and neurological handicap.

**Design and methodology (Data expected to collect, sample size and statistical analysis):**

Describe concisely the research design and methods for achieving these goals. Suggested length 2-3 paragraphs

We aim to collect data from at least 40 clinicians who are known to have or have had patients with severe inherited protein C deficiency. The participating clinicians will be invited to enter their data using the ISTH REDCap data collection system. The data can be obtained from the medical records of the affected child (children) and the mother and/or by interviewing the mother.

**Information about children with severe protein C deficiency**

Clinical features of the patient(s) with severe inherited protein C deficiency (to confirm diagnosis of severe inherited protein C deficiency)

Laboratory data eg protein C levels, mutation analysis (to confirm diagnosis of severe inherited protein C deficiency)

**Outcome measures and analysis:**
SSC Subcommittee Project/Collaborative Project

These would be the incidence of miscarriage and stillbirth in the study population and the incidence of previous neonatal death, which may have been due to undiagnosed severe protein C deficiency.

The data will not be subjected to statistical analysis. However, the incidence of miscarriage and stillbirth in the study population will be compared with the incidence of these conditions in that country.

**Study population (Inclusion, exclusion, eligibility) (patient population; recruitment of participating institutions/physicians and subjects; minimum number needed; expected number):**

Suggested length 2-3 paragraphs

This is an international study. Clinicians who have had patients with severe inherited protein C deficient patients have been identified from the literature, from networking at meetings and from Shire Pharmaceuticals (formerly Baxalta) who manufacture Ceprotin which is used to treat severe protein C deficiency. Patients have been identified in UK, USA, Canada, Australia, Germany, France, Netherlands, Spain, Switzerland, Turkey, United Arab Emirates, Saudi Arabia, Egypt, Oman, Algeria, Argentina and Singapore. All families who have had children with severe inherited protein C deficiency will be eligible. Patients with severe protein C deficiency due to other (acquired) causes (e.g., septicaemia, extreme prematurity, galactosaemia) will not be eligible. We hope to collect data on ~40 cases. Minimum number required 30 cases.

**Expected timeline:**

- Project stage/set up - 6 weeks
- Launch -12 week
- Duration – 12 months
- Finalization/analysis - 12 weeks
- Reporting - 12 weeks

Overall project timeframe Dec 2018- Dec 2019

**Expected outcomes (ie. publications):**

SSC communication and original article

**Description of project set/up and management, needed infrastructure and resources (summary):**

We will use the ISTH REDCap system for data collection. Dr Rezan Abdul – Kadir (Royal Free Hospital London), Dr Adrian Minford (retired paediatrician Bradford Royal Infirmary) will analyse the data, report to SSC and write the publication.

**References:**