

## Types I and III

### TRANSCRIPTION OF THE PRESENTATIONS TO TYPE I AND TYPE III FAMILIES AT THE 2008 AGSD(UK) ANNUAL CONFERENCE .

Given by

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#### TYPE I

##### **Notes on affected parts of the body**

1. About 50% of liver in Type I is fat and it appears typically pale pink, unlike a normal liver which is red. Fat is even apparent in the skin which can be seen in Type I patients. In Type I patients' carcinomas are always in adenomas and not in the liver itself. Signs of carcinomas are abdominal pain and rapid growth of the adenoma but there are no reliable parameters yet. Anaemia in many patients occurs with adenomas as they can prevent iron from being released for haemoglobin through inappropriate levels of Hepsidin. High Hepsidin prevents iron to taken up from the gut and decreases release from iron stores in the body

2. Patients do not appear to suffer from arteriosclerosis although they can have high levels of lipids, cholesterol and triglycerides.

3. Professor Smit considers that kidney problems leading to renal insufficiency are one of the major hazards of GSD Type I. The kidneys are enlarged because of glycogen storage and because of that- but not only because of that- the flow of blood is increased and this leads to an increase in kidney filtration. It begins before the age of five and reaches a peak at the age of fifteen. Because of the increased blood flow through the kidneys, as a result of the increased intra-renal pressure, holes appear in the kidney filter membrane and albumen will be lost in the urine. Protein (albumin) appearing in the urine will be the first sign. An ACE inhibitor will decrease the pressure so the albumen and protein loss in the urine may also decrease. Professor Smit gives an ACE inhibitor –if indicated- from age 3 to 4 years on. He uses it as a renopreservative treatment before problems in kidney function may start. It is expected that ACE inhibitors may also diminish the tendency towards fibrosis of the kidneys.

#### Management

It is very important for Type I patients to engage in some sport. Muscles can burn fat and bone density is increased.

Diets vary from country to country. Prof Smit recommends frequent meals with some fruit and milk every day. He also advocates the nasogastric tube as in his opinion it is a safe and excellent treatment in order to prevent from life-threatening hypoglycaemias and induce optimal growth. In the experience of the UMC Groningen there has only been one death and that was due to human error. Nocturnal tube-feeding eliminates the need for a night feed which has to be given if cornstarch is being used.

Cornstarch in Europe differs from Argo which is used in the USA .

Adults will generally need 2 gram cornstarch to 1 kilogram of body weight. In Adults but especially in children the optimal dose of cornstarch needs to be tested. If a child has a fever every one degree temperature rise in Celsius means that 10% more energy is being expended and therefore more carbohydrates must be given to compensate.

### **Type Ib**

Type Ib patients have the same symptoms as Type Ia with the added problems of bowel disease and infections.

A Type Ib baby is the same as a Type Ia baby until around a ½ year old. At that time the number of leukocytes (white blood cells) decreases and patients develop neutropenia. In some patients neutropenia may develop from the age of 6 years. The leukocytes that are present in Ib patients are not only low in numbers, they also move slowly and when bacteria are captured they have difficulties in digesting the bacteria... The drug GCSF causes the bone marrow to send out young active leukocytes which move fast and are able to kill the bacteria and thus prevent or cure from infection.

### **New survey**

A comprehensive report on Type I will be published next year. Doctors from many countries have collaborated and have logged in their patients details onto a central data base to provide the information for the report. It is hoped to have the details of 250 to 300 patients.

In April 2008 Prof Smit., Dr Lee, Dr Walters and Dr Weinstein met at Manchester during a clinical course for medics with an interest in metabolic diseases. They went over all the present guidelines for the diagnosis and treatment of Type I and adjusted them accordingly. These will be published in 2009 along with the results of the Type I survey.

### **TYPE III**

Prof Smit coordinates a large retrospective study on GSD 3. Patients from European countries and the US will be enrolled. The retrospective study should result in consensus guidelines on treatment and follow-up. At the present time there is no consensus. 80% of patients have Type 3a which affects the liver, muscles and sometimes the heart. Type 3b is just liver-related. 3c and 3d are extremely rare. Professor Smit has only seen one patient with 3d.

What is our current knowledge of GSD 3?

#### **Typical presentation of Type III patients**

Short stature

Enlarged liver

Obesity

Muscle deficiency (Type 3a)

#### **Problems occurring in Type 3 patients.:**

Hypoglycaemia

High ketone bodies in blood and urine

High lipids

Uric acid concentration in some patients can be elevated

**Diagnosis**

An enlarged liver is the first symptom and is generally noticed at about six months. Hypoglycaemia occurs after a year as the intervals between feeding the child become longer. A few patients are found to have a large spleen. The liver will decrease in size as the patient reaches adulthood.

Hypoglycaemia is not so prevalent in an adult. Graphs have been produced to calculate accurately the amount of carbohydrates needed by an individual patient. However for a fever there should be an increase of 10% of carbohydrate-intake for every degree rise in temperature.

Professor Smit's young patients use a nasogastric tube (he does not use European cornstarch on babies) and a high protein diet and they grow well.

**Complications that may occur which are being studied for I in the new consensus study**

*It must be stressed that these are complications that **MAY** arise*

**Growth**

36% of patients in a study undertaken in 1990 were below normal height.

**Tendency to develop cirrhosis**

Cirrhosis has been seen in Type 3 patients and can lead to carcinomas in the liver. The consensus study will hopefully find the incidence of having a cirrhotic liver and whether poor metabolic control may contribute to this condition. Next to this guidelines for precaution need to be discussed to avoid this complication: such as improvement in the dietary treatment leading to an optimal metabolic control.

**Bone density**

Low bone density is not found in many of Type 3 patients. Dietary measures and exercise may help to improve bone density.

**Myopathy****Cardiomyopathy**

Protein enrichment could help cardiomyopathy but it still has to be proved and there is no evidence based proof as yet.

**Myopathy in peripheral nerves**

So far this has only been found in Bedouin patients where there is obviously a mutation link. In these patients glycogen deposits were detected in peripheral nerve tissue.

**Diabetes**

Diabetes can occur in Type 3 patients and the consensus study will look into this.

**Arthrosclerosis**, no information yet available.

**Renal problems**, no information yet available.

Metabolic centres from all over the world are taking part in the consensus study on GSD 3 and it is hoped that the details of some 300 patients will be enrolled. A newly developed data base is being used. Ultimately consensus guidelines on treatment and follow-up on GSD 3 will be published. Doctors can only look at the details of their own patients but can supply information without giving the names of the patients and can update this when necessary. Most importantly they will be given information on what checks they should carry out as deduced from the data collected.

**Research Projects**

Research is being undertaken using stable isotope labelled metabolites in search for a better understanding of the intermediary metabolism in GSD 3 patients. Stable isotopes have a different mass than the “normal” metabolites like for instance glucose. Next to this specific Mouse models are being developed to study the effects of aging on the complications in GSD 3, as the life span of a mouse is very short in comparison humans.

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