

## SUMMARY OF PRESENTATION BY DR PRIYA KISHNANI OF DUKE UNIVERSITY TO TYPE 3 FAMILIES

Doctor Kishnani has had an interest in Type 3 GSD for thirty years as her mentor Professor Y.T.Chen cloned the Type 3 gene.

Dr Kishnani gave updates on the following topics

Heart

Liver

Role of the biomarker

Animal models.

The gene for Type 3 is one of the biggest ones. It has 35 compartments compared with the Type I which has 5 compartments

Dr Kishnani gave a short explanation of the chemistry of the debranching enzyme in Type 3.

.The enzyme in Type 3 needs two activities to work for the enzyme to be effective.

The first activity is transferase, (transferring glucose molecules)

The second occurs at the branch point where phosphorylase cannot break down the glycogen completely.

The result is too much glycogen in the liver and also in the muscles and heart in Type 3a.

This glycogen has an abnormal structure which can act like a foreign body and in time can become a problem.

She listed the features of Type 3a

Large liver

Growth difficulty

Low blood glucose

High lipids and cholesterol

Skeletal involvement

Muscle and heart involvement.

Hypoglycaemia is less apparent in Type 3a compared with Type I as glucose can be obtained from the breakdown of glycogen plus that made from proteins and amino acids.

It also gets less with time.

A child with good metabolic management will have a large liver due to the abnormal structure of glycogen .

Duke concentrates on providing good metabolic control to assist growth, the correction of hyperlipidemia and the correction of ?? (*Priya, I did not manage to hear this*)

Duke has a patient aged 55 with Type 3b and several Type 3a patients in their 50's and 60's.

In these patients there has been no correlation between the amount of protein expressed and the clinical severity.

Also the severity of the skeletal and heart muscle is not predictable

Liver transplant is only necessary if there is progressive liver damage or progressive liver cirrhosis.

This will only occur in adults in their 60's who did not have good treatment in their youth and even then it will only occur in very few cases.

The bulk of children at Duke with Type 3a do really well but they are still monitored regularly.

Hepatic adenomas are much rarer in Type 3 than in Type 1 say 25% but of the 36 patients at Duke only 2 had adenomas,

The majority of Type 3a children have asymptomatic enlargement of the heart due to thickening of the heart muscles but there is no correlation with skeletal muscle symptoms. In the 1990's Dr Lee looked at 32 patients and found that 40% had thickness of the heart wall but this was not followed up. Dr Kishnani stated that an ECG and a baseline echo diagram once a year would demonstrate if the thickness changed the function of the heart. If necessary beta blockers could be used but with caution as they provoke hyperglycaemia. Overall she felt that the rate of progression of the thickness was very slow and the heart function was not impaired.. There have only been 2 transplants.

### **Biomarker**

A biomarker tracks disease in a non-invasive way. Glucose4 is a non invasive biomarker of glycogen accumulation There has been good clinical correlation when it has been used in Type 2 patients.

### **Animal models**

Curly coated retriever puppies with Type 3a have been bred and are being used for research purposes. Ironically these dogs are too big and will have to be bred down whereas the Type Ia maltese breed is too small and has been crossbred up with beagles to produce a malteagle! A mouse model is also being worked on. At Duke the malteagles are used to study gene therapy in Type Ia and the retrievers are used to study enzyme replacement therapy in Type 3. (*Priya, I hope this is correct*)