A GENETIC APPROACH FOR RARE INHERITED METABOLIC DISEASES

DR NTOMBENHLE LOUISA BHENGU
DEPARTMENT OF HUMAN GENETICS
CLINICAL UNIT

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

NATIONAL HEALTH
LABORATORY SERVICE

INHERITED METABOLIC DISEASES (IMD)

- Inborn errors of metabolism due to enzyme deficiency
- Single gene disorders with serious clinical/genetic implications as they are incurable in most cases
- Inherited mainly in AR manner but can be X-linked recessive/dominant /rarely due to mitochondrial inheritance
- REQUIRE A GENETIC APPROACH for proper care.
- Process involves thorough history taking, clinical examination and investigation to make accurate diagnosis
- Confirmation of diagnosis with biochemical and /or molecular testing is important for future genetic counselling and
- Multidisciplinary Care and Support Groups

CASE 1 –Krabbe Disease

- 9 months old baby boy, non-consanguineous african parents
- Presented with neuro-regression from 3-5 months of age
- Extreme irritability, loss of vision, feeding problems with FTT.
- Progressively encephalopathic, ?seizures
- Raised CSF protein. Optic atrophy.
- Died at 10 months
- Previous sibling similar presentation and also demised before one year without Dx.
- Brain CT showed dilated optic nerves ? Optic glioma = NFI
- Evidence of café au lait spots

Investigations

Brain MRI- Both for children (8 months)

- Bilateral optic nerves enlargement (and other cranial nerves)
- Marked brain atrophy –cortical and gray matter
- Increased intensities in the thalamus [Leukodystrophy]

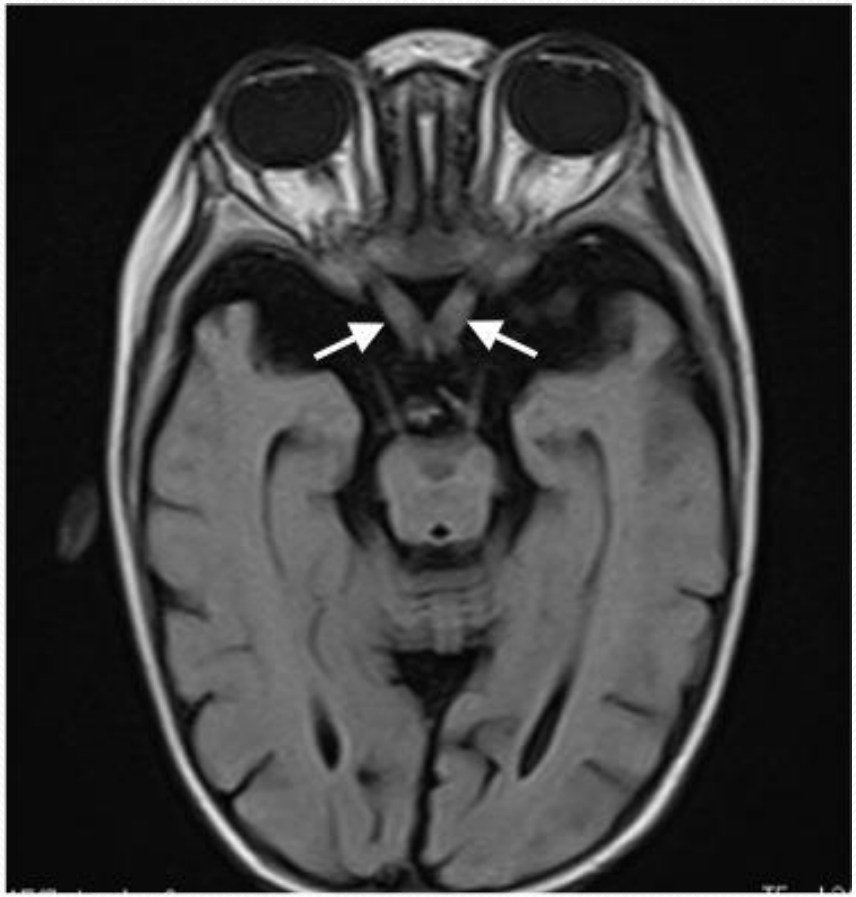
Metabolic work up (Philadelphia)

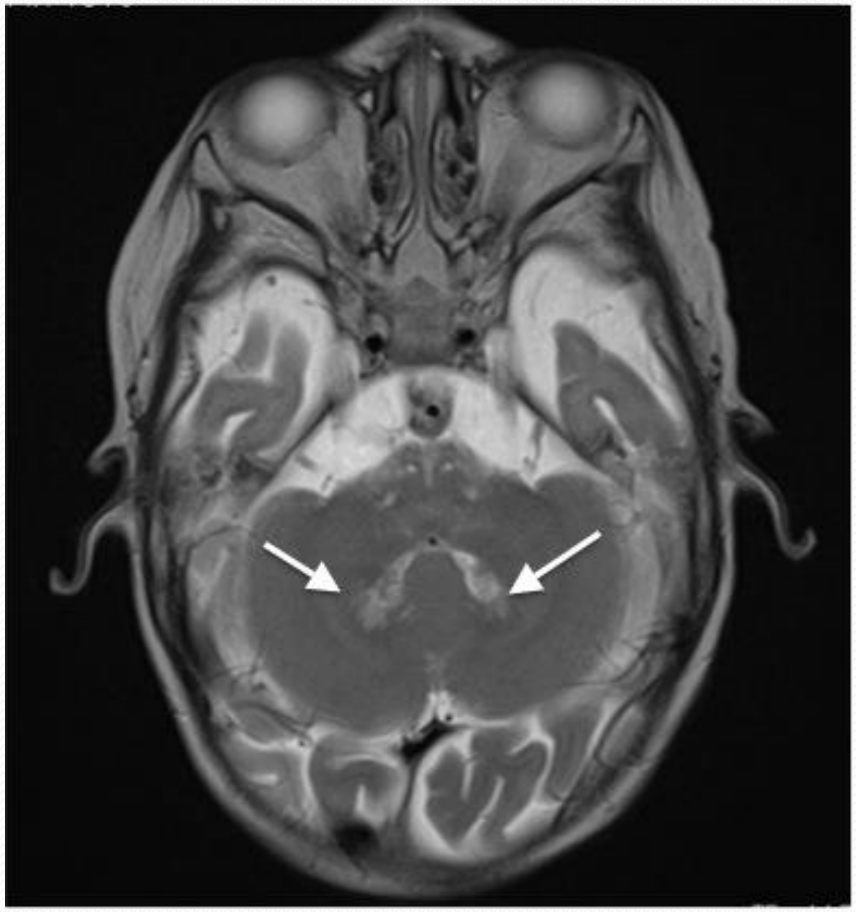
- **Very low levels of Galactocerebrosidase –in keeping with KRABBE DISEASE**

DNA analysis : No mutations were found in GALC gene by gene sequencing in CT

- Therefore unable to offer carrier testing/ prenatal diagnosis and pre-implantation Genetic Diagnosis

Hypertrophy of optic nerves and leukodystrophy





CASE 2- Krabbe disease

- Non-consanguineous white parents
- Previously lost their son at 4 months of age
- Neuro-regression and hypotonia
- Maternal history of recurrent miscarriages x4
- Dx of KD made on enzyme analysis and confirmed on DNA mutation analysis (done in Belgium -547 euros)
- Counselled as AR condition with 25% recurrence risk
- Prenatal Diagnosis and Pre-implantation Genetic Diagnosis (PGD)
- Referred to Genesis genetics clinic

PGD Results in Case 2

- Pregnancy induced by IVF - done by Vita Lab
- Single cell PGD done -5 samples from embryos sent to Genesis Genetics in US
- Familial mutations were tracked
- Results: In 4 samples -mutant parental alleles observed (homozygous mutants) **-30 kb common deletion**
- One sample –mutant paternal and normal maternal haplotypes =Heterozygous carrier =unaffected
- Selected "normal" embryo for re- implantation during a subsequent natural cycle
- CVS /Amniocentesis recommended to confirm normal fetus
  -due to possibility of mosaicism in the embryo
- Successful pregnancy (**usually 30% chance per cycle**)
- **PGD is expensive and time-consuming but avoids TOP**
- **PGS done for aneuploidy screen in AMA, recurrent miscarriages**

KRABBE DISEASE (Globoid cell Leukodystrophy)

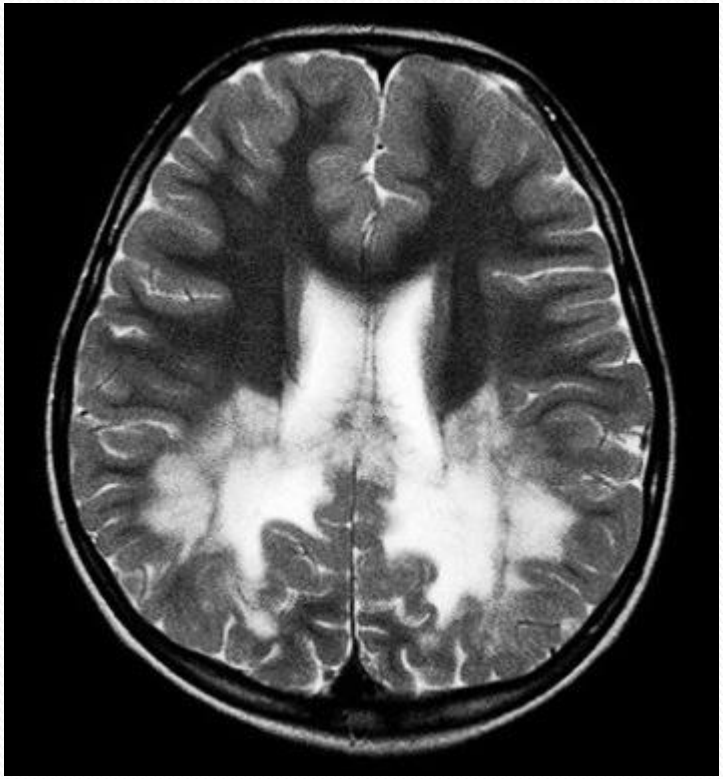
- AR inborn error of metabolism caused by deficiency of the enzyme **galactosylceramidase (galactocerebrosidase).**
- **A Lysosomal enzyme** involved in the catabolism of galactosylceremide, a major lipid in myelin, kidney and epithelial cells of small intestines and colon.
- ENZYME DEF results in the build up of undigested fats affecting growth of nerve's protective myelin sheath and causes severe degeneration of mental and motor skills.
- GALC gene locus is at 14q31 and has 17 exons **-30kb common deletion** in the homozygous state is associated with infantile onset disease

(allele frequency in KD is 50% in Dutch patients and 35% in other non-Dutch European patients and ? in Blacks

CASE 3 –X-linked Adreno-leukodystrophy (X-ALD)

- A 4 year old African boy presented with progressive neuro-regression and seizures from 18 months and developed spastic quadriplegia, bed ridden and death
- **Brain CT/MRI** showed evidence of demyelination and brain atrophy in keeping with X-ALD
- **Biochem**: VLCFA assay-Raised C24:C22 and C26:C22 and raised ACTH in keeping with adrenal insufficiency
- **Mutation analysis**: Positive for one ABCD1 mutation
- Cascade testing –mother (was tested positive) and sisters, other males (future)
- Males and carrier females are at increased risk of Adrenomyeloneuropathy (AMN) –2nd phenotype, late onset 30-40 years
- Peroxisomal storage disorder –ABCD1 gene on Xq28

MRI in X-ALD - Prominent T2 hyperintensities in the parieto-occipital region



CONCLUSION

- Important to make accurate diagnosis
- Molecular diagnosis assist in finding a specific familial mutation which allows the following:
- Confirmation of diagnosis
- Counselling for Prenatal Diagnosis, Pre-implantation genetic diagnosis (PGD),
- Carrier testing /cascade testing
- Future Newborn screening

ALL PATIENTS WITH RARE DISEASES should be referred to Genetic Clinic