Clinical characteristics and long term follow up of 17 patients with permanent neonatal diabetes due to PTF1A distal enhancer mutations

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OBJECTIVES

- Pancreas transcription factor 1 alpha (PTF1A), encoded by PTF1A gene is a beta helix loop (bHLH) protein
- Involves in the development of pancreas and cerebellar neurogenesis.
- Mutations of PTF1A cause permanent neonatal diabetes (PNDM), pancreas agenesis and cerebellar agenesis.
- PTF1A enhancer mutations have been reported to cause PNDM and isolated pancreas agenesis.
- We evaluate the phenotype and genotype characteristics and long-term follow up of 17 patients with PNDM and isolated pancreas agenesis due to PTF1A distal enhancer mutation.

METHODS

- Neonatal diabetes was defined as diabetes presented within the first 6 months of life.
- Presenting clinical and biochemical characteristics were reviewed from the hospital files of the patients.
- A molecular genetic analysis was performed to all the patients and their parents who a DNA sample was available.
- The latest growth, developmental milestones and metabolic characteristics were re-evaluated once applicable.

RESULTS

- Number of patients recruited was 17.
- Presenting and follow up characteristics of patients are summarized in Table 1
- Majority of cases had severe IUGR
- Birth weight SDS was negatively correlated with gestational age (r=0.827; p=0.000).
- All patients had clinical signs of exocrine pancreas insufficiency and pancreas agenesis/hypoplasia in radiological imaging.
- A low faecal elastase was measured in 8 out of 9 patients.
- Insulin therapy and pancreas enzyme replacement were introduced to all patients.
- A transient, but markedly elevated ferritin level was detected in all patients who ferritin levels had been measured at the neonatal period.
- In the molecular genetics analysis, the most common mutation was (Figure 1); PTF1A distal enhancer g.23508437A>G which was detected in 12 cases.
- PTF1A distal enhancer g.23508365A>G was detected in 2 cases.
- PTF1A distal enhancer g.23508365G>T mutation in a single case

CONCLUSIONS

- In this large series of 17 cases with PNDM due to homozygous distal enhancer PTF1A mutations, presence of severe IUGR, isolated pancreas agenesis/hypoplasia and exocrine pancreas insufficiency in all cases suggested a good phenotype-genotype correlation.
- Although was not measured in all subjects, markedly elevated ferritin level and its role in the phenotype of patients remain unknown and require to be further elucidated.
- Finally, although, all were replaced using pancreas enzyme, majority of cases failed to catch up growth.
- This can be attributed to poor compliance to the enzyme replacement, but, still requires further investigations to clarify the underlying exact mechanism