OUTCOME OF SYMPTOMATICALLY DIAGNOSED UREA CYCLE DEFECTS IN INDIA

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BACKGROUND

Urea cycle disorders (UCDs) are amongst the most common inborn errors of metabolism[1]. The incidence and outcome of this group of disorders in India is not known. The aim of the study was to determine the outcome of symptomatically diagnosed UCD patients.

METHODS

This is a retrospective study on the data of 76 patients suspected to have UCD for the period of 10 years (2009 to 2019). We suspected UCD in 76 Patients (42 males and 34 females). Biochemical and genetic studies were performed to ascertain the diagnosis. Plasma amino acids and urine orotic acid analysis were performed by UHPLC. Argininosuccinic acid was determined by LCMSMS. Acyl carnitines were analyzed by TMS and Urine organic acids by GCMS to rule out other disorders. UCD was confirmed in 41 patients (26 males and 15 females). Outcome and follow-up data for each of these patients was analyzed.

RESULTS

In our cohort of n=76, we diagnosed Argininosuccinate synthase Deficiency (ASSD) (Citrullinemia Type I) in 21 patients (11 males and 10 females), Argininosuccinate lyase deficiency (ASLD) (Argininosuccinic aciduria) in 10 patients (8 males, 2 females), Ornithine transcarbamylase deficiency (OTCD) in 4 patients (3 males and 1 female), Carbamoyl phosphate synthetase 1 deficiency (CPSD) in 1 male, N- acetyl glutamate synthase (NAGS) deficiency in 2 patients (1 male and 1 female) and Arginase deficiency (ARGD) in 3 patients (2 males and 1 female).

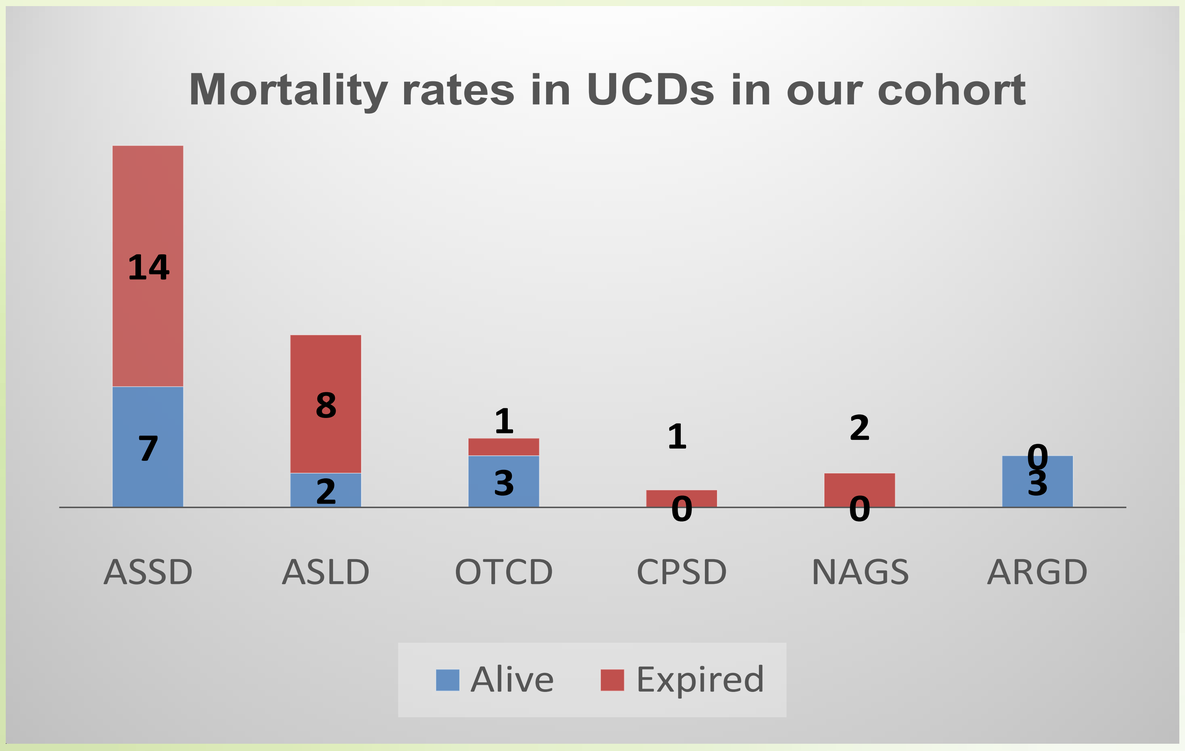
Disease	Male	Female	Total
CPS1	1	0	**1**
NAGS	1	1	**2**
OTCD	3	1	**4**
ASSD	11	10	**21**
ASLD	8	2	**10**
ARGD	2	1	**3**
Total	**26**	**15**	**41**

Mortality in our cohort was very high (63%) with 66% for ASSD (14/21), 80% for ASLD (8/10), 25% for OTC (1/4), and100% for CPSD (1/1) and NAGS (2/2). OTC was diagnosed in 3 males in our cohort and 2 of them are surviving well.

Disease	Mortality
ASSD	66% (14/21)
ASLD	80% (8/10)
OTCD	25% (1/4)
CPSD	100% (1/1)
NAGS	100% (2/2)
ARGD	0% (0/3)
Total	63% (26/41)

DISCUSSION

In India there is no universal new born screening therefore the diagnosis of UCD is usually in the symptomatic stage leading to adverse neurological outcomes. Injectable sodium phenylbutyrate, sodium benzoate and arginine and also oral sodium phenylbutyrate and carbamylglutamate are not available and not affordable for most of the patients. Even hemodialysis is not available at all hospitals and management is usually by peritoneal dialysis. All these factors affect the outcome in our population. In our cohort citrullinemia is the commonest urea cycle disorder seen and mortality is very high as compared to other countries. Lack of nationwide new born screening and unavailability of crucial ammonia scavengers affects the mortality rates and long term neurological outcome in our population. Liver transplant is now being considered in many cases of Urea Cycle Defects as the first line of treatment.



Disease	Good neurological outcome	Poor neurological outcome	Lost for follow up
ASSD	2	2	3
ASLD	1	0	1
OTCD	3	0	0
CPSD	0	0	0
NAGS	0	0	0
ARGD	1	2	0
Total	7	4	4

In our cohort, 11 patients are alive and are being monitored regularly with good neurological outcomes in 7 patients and poor neurological outcome in 4 patients. 4 patients are lost for follow-up and the remaining 26 patients expired. Two patients with citrullinemia type I underwent liver transplant (at 3 months and 6 yrs of age). Both these patients are well after the transplant and on normal diets.

CONCLUSION

The outcome of UCDs in our population is very poor with high mortality (63%) and poor neurological outcome in most of the patients. This can be due to unavailability of new born screening and symptomatic detection of most of the patients.

CONFLICT OF INTEREST : None

REFERENCES

1. Brusilow SW, Horwich AL. Urea cycle enzymes. In: Valle D, Beaudet AL, Vogelstein B, Kinzler KW, Antonarakis SE, Ballabio A, Gibson K, Mitchell G, eds. The Online Metabolic and Molecular Bases of Inherited Disease.

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