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ARTICLE

Etiological Spectrum with Diagnosis and Prognosis of Central Diabetes Insipidus needs Long Term Followup: A Single Centre Experience

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ABSTRACT

Introduction: Central Diabetes insipidus (CDI) is a rare disorder caused by vasopressin deficiency characterized by the excretion of copious volumes of unconcentrated urine. **Objective:** To assess the etiological, clinical, biochemical and radiological spectrum of Central DI in our institute and long term follow up of these cases. **Material and Methods:** 32 patients with Central DI admitted in Department of Endocrinology, Guwahati Medical College, Assam in the last 2.5 years were included. Detailed clinical assessment, biochemical evaluation and MRI (Magnetic Resonance imaging) brain were done in all the patients. Central DI without any identifiable cause was considered Idiopathic and those with structural lesion in hypothalamic pituitary region were considered organic. **Result:** Idiopathic CDI was present in 12(37.5%) patients and 20(62.5%) patients had organic CDI with acute onset of presentation. 12(60%) patients with organic CDI present with neurological symptoms but 8(40%) patients had no neurological symptoms even with organic cause. Pituitary dysfunction was common in organic CDI as compared to idiopathic CDI. Paediatric patients commonly present with organic cause for CDI with low cortisol most common hormonal deficit. One patient of idiopathic CDI with normal stalk thickness at baseline presented with clinical and radiological features of LCH(Langerhans cell histiocytosis) on follow up. **Conclusion:** Organic CDI more likely to have acute onset of presentation than idiopathic CDI and even in absence of neurological features. Paediatric patients commonly have organic cause for CDI. We propose the paramount importance of long-term clinical follow-up and reassessment of endocrine function in patients with CDI for definitive diagnosis of autoimmune and inflammatory causes of idiopathic CDI and timely treatment of pituitary hypofunction.

1. Introduction

Diabetes insipidus is a rare disease with a non-univocal reported prevalence of 1:25,000 [1] and characterized by the excretion of copious volumes of unconcentrated urine, results from either impaired vasopressin secretion, impaired renal response(-nephrogenic), excessive fluid intake (primary polydipsia) or increased metabolism of the hormone (gestational diabetes insipidus). A combination of hormonal, clinical, and neuroradiologic evaluation is required for differentiation between their causes, pathophysiology, and for effective

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management. Vasopressin is synthesized by neurons of the hypothalamic paraventricular and supraoptic nuclei and secreted by the posterior pituitary gland [2]. Central nervous system (CNS) tumours, post-neurosurgical or accidental trauma, autoimmune, infiltrative diseases and rarely genetic mutations are known causes of central DI [3]. There are many diagnostic and therapeutic challenges in CDI which may result in delayed during evaluation for more common aetiologies of polydipsia and polyuria, and often requires formal water deprivation testing [2]. After the diagnosis, further work-up to determine the aetiology of CDI and additional pituitary hormone deficiencies is required; however, there is lack of clear guidelines regarding laboratory and imaging studies to obtain and at what intervals these investigations to be repeated. Desmopressin (DDAVP) with an extended duration of action is a synthetic analog of arginine vasopressin and is the mainstay of therapy for CDI. Given the number of diagnostic and therapeutic challenges associated with CDI, we performed a retrospective chart review of a cohort of patients with CDI followed at the in order to describe our experience and to contribute further to generalizable knowledge about the diagnosis and management of CDI.

2. Method

Study was conducted at Guwahati Medical College and Hospital. The aim was to characterize the etiological spectrum of central DI and to determine whether clinical, biochemical and specific MRI characteristics(pituitary stalk thickness, posterior pituitary bright spot) could provide clinician guidance with regard to the etiology and follow up of these patients.Total of 32 patients attending department of Endocrinology over a period of 2.5 years with history of polyuria and polydipsia were included in study after obtaining written informed consent. Patient with history of Diabetes mellitus, Head injury, irradiation, diuretics, renal failure, RTA, Hypercalcemia, hypokalaemia, transient Diabetes insipidus were excluded from the study. Central DI without any identifiable cause was considered Idiopathic and those with structural lesion in hypothalamic pituitary region were considered organic REF. Patient characteristics age, sex duration of clinical symptoms prior to diagnosis in those presenting with CDI, pituitary hormone evaluation, family history, neuroimaging study results, and pathology findings were recorded. The frequencies of various aetiologies of CDI as well as characteristic magnetic resonance imaging (MRI) findings were determined. CDI was diagnosed either by water deprivation testing or by the presence of concurrent polyuria, hypernatremia, elevated serum osmolality, low urine osmolality, and low urine specific gravity. The prevalence of anterior pituitary hormone deficiencies at each patient's presentation and the incidence of hormone deficiencies acquired later in the disease course were also evaluated over period of 12 months. The hormonal deficiency was confirmed by laboratory evidence of insufficient hormone production.

3. Results

Total of 32 subjects included in study (14 male and 18 female), mean age was 37.2±18.8 years (Table 1). The mean duration of symptoms in our study group was 15.4±11.2 months with organic CDI having more acute presentation as compared to Idiopathic CDI (12months vs 21 months). All patients underwent MRI Brain and 12 (38%) patients on the basis of absence of any identified organic cause were diagnosed as Idiopathic CDI (Figure 1) and 20 (68%) patients with organic aetiology were diagnosed as organic CDI. The organic causes includes craniopharyngioma 7 (22%), granulomatous 3 (9%), Rathke's cyst 2 (6%), pituitary adenoma 6 (19%), meningioma 1 (3%), glioma 1(3%).In our study group most of children had organic CDI(craniopharyngioma 3 patients and glioma 1 patient). Polyuria and polydipsia was the most common presenting complain present in all the subjects (Table 2). Other complains includes headache 12 (40%), vomiting 6 (20%), seizure 5 (16%), visual disturbances 3 (10%), short stature 2 (6.6%). Neurological features and anterior pituitary hormonal deficiency were common in organic CDI as compared to Idiopathic CDI but some patients in organic CDI present with hormonal deficiency even in absence of neurological features.16 patients underwent formal water deprivation test while rest of patient already fulfilled criteria for Diabetes insipidus. Biochemically hyperprolactinemia was most common hormonal derangement and present in 15 patients (46%), other deficiency includes hypothyroidism 11 patients (34%), low cortisol 13 patients (40%), hypogonadism 8 patients (25%) and GH deficiency 8 (25%) patients (Figure 2). Pituitary bright spot was absent in all patient with Idiopathic DI as compared to 13(65%) of organic DI (Table 3). 8 (40%) patients of organic DI had pituitary stalk thickening as compared to 1(8.3%) patient of Idiopathic DI. On 12 months follow up 2 patients in Idiopathic DI had pituitary stalk thickening with progressive pituitary hypofunction in the form of 2 patients had hypothyroidism at 6 month and 1 patient developed hypogonadism at 12 months follow up (Table 4). One of the patient initially diagnosed with Idiopathic CDI developed progressive skeletal manifestation of LCH in the form of proptosis of unilateral eye along with ear discharge at 12 month follow up which was later diagnosed with bone marrow biopsy and radiological imaging (Fig-

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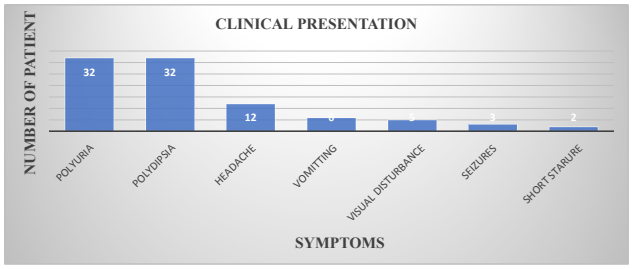
ure 3). At follow up of 12 month 2 additional patients in organic CDI lost pituitary bright spot and 1 patient developed new onset low cortisol and 2 patient hypothyroidism on 6 month and 12 month follow up respectively (Table 4). Low cortisol (75%) was the most common hormonal deficiency in paediatric patients followed by GH deficiency (62.5%) and hypothyroidism (50%), hyperprolactinemia (50%), hypogonadism (37.5%). All patients with CDI were treated with either nasal or oral DDAVP.

Table 1. Baseline characters and aetiology of CDI

N=32	BASELINE CHARACTERISTICS
AGE (YEARS)	37.2±18.8
SEX M:F	14:18
Duration of symptoms(months)	15.4±11.2
Etiology- Idiopathic Craniopharyngioma Granulomatous Rathke's cyst Pituitary adenoma Meningioma Glioma	12 7 3 2 6 1 1

Table 2. Presenting complain of subjects



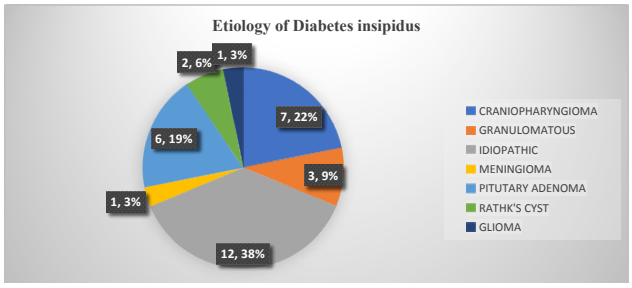


Figure 1. Etiology of CDI

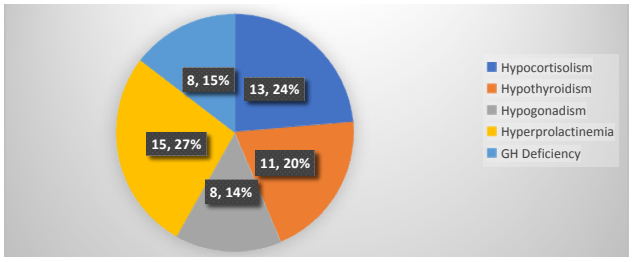


Figure 2. Hormonal profile of Subjects

Table 3. Radiological and hormonal profile of Idiopathic and organic CDI

	IDIOPATHIC CDI(N-12)	ORGANIC CDI (N-20)	P VALUE
Age	41±17	30.6±18.5	-
Sex(M:F)	7:5	7:13	0.3
Duration of symptoms(month)	**21 (10-48)**	**12 (6-24)**	**0.04**
Short stature	0	2 (28%)	NS
Neurological features	**2 (16%)**	**12 (60%)**	**0.04**
P pituitary bright spot Absent	12 (100%)	13 (65%)	-
Pituitary Stalk thickening	1 (8.3%)	8 (40%)	-
Hypogonadism	0	8 (40%)	0.02
Hyperprolactinemia	1 (8%)	14 (70%)	0.002
Hypocortisolism	1 (8%)	12 (60%)	0.01
Hypothyroidism	1 (8%)	10 (50%)	0.04
GH Deficiency	1 (8%)	7 (35%)	0.05

Table 4. Follow up of Idiopathic and organic CDI

	Idiopathic central diabetes insipidus(N-12)			Organic central diabetes insipidus(N-20)		
	Baseline	6 month	12 month	Baseline	6 month	12 month
Pituitary stalk thickening (Number of patients)	1	-	2	8	-	8
Bright spot present	0	-	0	7	-	5
Bright spot absent	12	-	12	13	-	15
Hypothyroidism	1	2	2	10	10	12
Hypogonadism	0	0	1	8	8	8
Hypocortisolism	1	1	1	12	13	13
hyperprolactinemia	1	1	1	14	14	14
GH deficiency	0	0	1	7	7	7

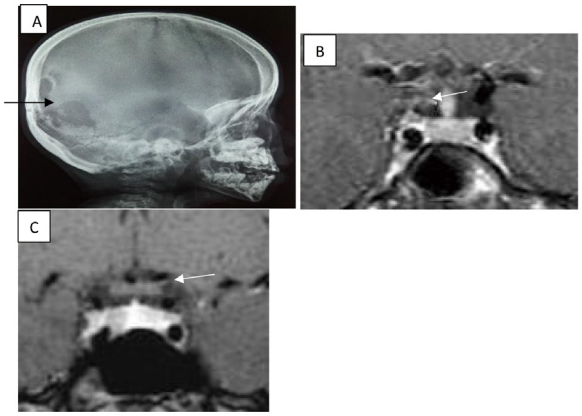


Figure 3. Cranial X ray with MRI images of subject with LCH

Notes: (Image A) X ray skull showing punched out lesion involving occipital and temporal region (Black arrow). T1W MRI image showing

normal pituitary stalk at baseline (image B white arrow) which shows thickening at 12 months follow up (image C white arrow).

4. Discussion

In our study 12(38%) patients had Idiopathic DI as compared to 20(68%) patients with organic DI. In a similar study Mohamad Maghnie[9] evaluated central diabetes insipidus in children and young adults and found 52% had idiopathic DI and intracranial tumour in 22% patients which is similar to our study group (28%). Natascia Di Iorgi [3] on the other hand found 71.8% with a presumable idiopathic form of CDI and 28% organic DI at presentation. In our study, organic DI subjects had significantly more acute presentation of symptoms like headache and visual disturbance (p-0.04). In our study, craniopharyngioma was the most common organic cause of CDI in paediatric patients (6 out of 8 patients), which was very similar to study by David Werny [10] in paediatric patients where most common single diagnosis was craniopharyngioma (25.2%). In our study anterior pituitary hormonal deficiency was present at diagnosis in 14(70%) patients in organic CDI as compared to 1(8%) patient in Idiopathic DI group which is similar to study by Masri-Iraqi H [11]. Natascia Di Iorgi [3] on the other hand showed that out of 61 idiopathic DI 35 patients (81.4%) showed at least 1 anterior pituitary defect within the first 2 years. Hee Joung Kim [12] found that 6 patients (20%) out of 30 Idiopathic DI had deficits in anterior pituitary hormone at diagnosis. The most common hormonal abnormality in our study was hyperprolactinemia 15(46%) patients, followed by low cortisol 13(40%) patients, hypothyroidism 11(34%) patients, hypogonadism 8(25%) patients, GH deficiency 8(25%).In paediatric patients low cortisol (75%) was the most common hormonal deficiency followed by GH deficiency(62.5%) which is in contrast to study by David Werny [10] and Janel D [13] where GH deficiency was the most common concurrent hormone deficiency followed by ACTH deficiency and TSH deficiency. On follow up of idiopathic DI 6 monthly, 2 patients in Idiopathic DI had pituitary stalk thickening with progressive pituitary hypofunction in the form of 2 patients had hypothyroidism at 6 month and 1 patient each developed hypogonadism and GH deficiency at 12 months follow up. One of the patient initially diagnosed with Idiopathic DI developed progressive skeletal manifestation of LCH (Langerhans cell histiocytosis) in the form of proptosis of unilateral eye along with ear discharge at 12 month follow up which was later diagnosed with bone marrow biopsy and radiological imaging. David Werny [10] In 22 patients with initially idiopathic CDI, four were found to have an underlying cause on follow up of 1.6 years and found that no concerning MRI changes were detected after 3 years from initial CDI diagnosis. Natascia Di Iorgi [3] on the other hand in 61 idiopathic CDI patients, 11(13%) received a specific diagnosis within 2.5 years. Our patient had normal stalk thickness at initial diagnosis which is in contrast to David Werny [10] study where the percentage of patients with an underlying cause was higher in those with initial pituitary stalk thickening. We didn't find any change in size of pituitary gland of patients of idiopathic DI at follow up of 12 months while Natascia Di Iorgi[3] found a change in the size of anterior pituitary on follow up MRI scan. In our study pituitary bright spot was absent in 13(65%) patients of organic CDI and 8(40%) patients had pituitary stalk thickening. At follow up of 12month, 1 patient in organic CDI developed new onset low cortisol and 2 patient developed hypothyroidism which underscore the importance of endocrine follow up in these patients.

5. Conclusion

(1) In conclusion, children and adults with organic central diabetes insipidus has acute onset of symptoms as compared to idiopathic CDI

(2) Organic CDI should be suspected even in the absence of neurological features

(3) Diagnosis of idiopathic CDI in children's should be made with extreme caution because of high frequency of CNS malformations and organic cause, and only after extensive evaluation, including MRI of the brain even in those with normal pituitary stalk thickness

(4) Careful monitoring of signs or symptoms of organ involvement by LCH is recommended after the diagnosis of idiopathic CDI

(5) Continued screening for endocrine dysfunction is warranted for timely diagnosis of hormonal deficiency and appropriate treatment, though further studies are needed to determine the most appropriate screening interval

(6) We suggest systematic neuroimaging, endocrine follow-up for definitive diagnosis of autoimmune and inflammatory causes of idiopathic CDI and timely treatment

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