Central diabetes insipidus in children: role of GH antibodies

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INTRODUCTION AND OBJECTIVES:

Central diabetes insipidus (CDI) in children is caused by brain tumors, Langerhans cell histiocytosis (LCH), trauma, infections, or genetic abnormalities in about 60% of the cases. In the remaining 40%, CDI is idiopathic even after detailed clinical and radiological investigations. CDI is often associated with anterior pituitary hormone defects. Disclosing the underlying condition early would allow clinicians to avoid unnecessary tests and to improve patient care.

Aim of the study was to assess whether measurement of serum antibodies against human growth hormone (GH) could aid in the identification of the etiological factors for CDI.

METHODS

We examined the clinical, radiological and biochemical features of 97 patients (49 males) being treated at a single centre (Gaslini Hospital, Genoa, Italy) between March 2000 and May 2018. 49 patients (50.5%) were diagnosed with sellar tumor, 5 pts (5.2%) had a genetic form, 10 pts (10.3%) had LCH, 32 pts (33.0%) had idiopathic CDI, 1 pt had pituitary abscess. Median age at diagnosis was 8,9 (5,9-12,2) years, median follow-up duration 8.5 (12.9-23.8) years.

65 patients were tested for anti-nGH antibodies (ELISA) at Department of Pathology, Johns Hopkins University (Baltimore, MD).. Of them, 36 were females and 29 males. Their diagnosis upon detailed clinical and morphological follow up was idiopathic (No.=31), brain tumor (No.=24), LCH (No.=6), genetic defects (No.=3), or pituitary abscess (No.=1). The median age at diagnosis and median follow up time were 8.9 and 8.5 years, respectively. Brain MRI and studies of anterior pituitary functions were performed in all patients at baseline and on follow up. Serum antibodies against native human GH were measured by a in-house ELISA assay where values below 50arbitrary units per mL are considered negative. In 8 children two serum collections were available and in 4 three, for a total of 81 sera.

Antibody result was divided into three categories: negative (<50 AU/mL), mild positive (50-100 AU/mL), strong positive (>100 AU/mL). Patients were tested for anterior pituitary hormone defects based on standard clinical practice.

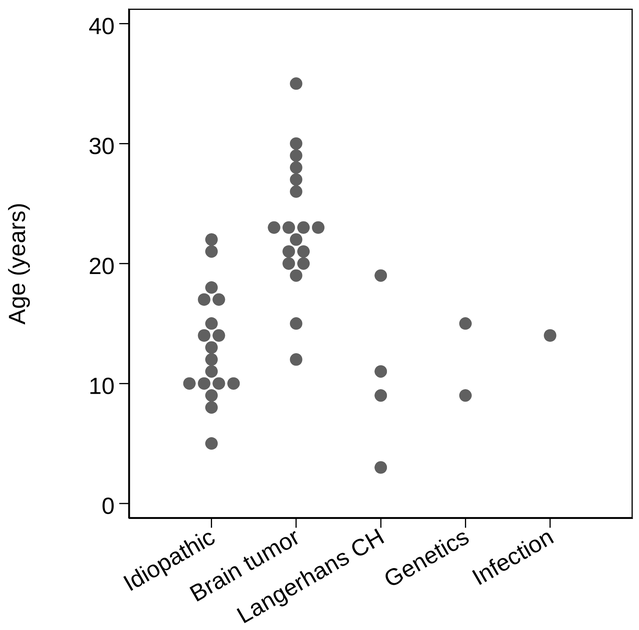
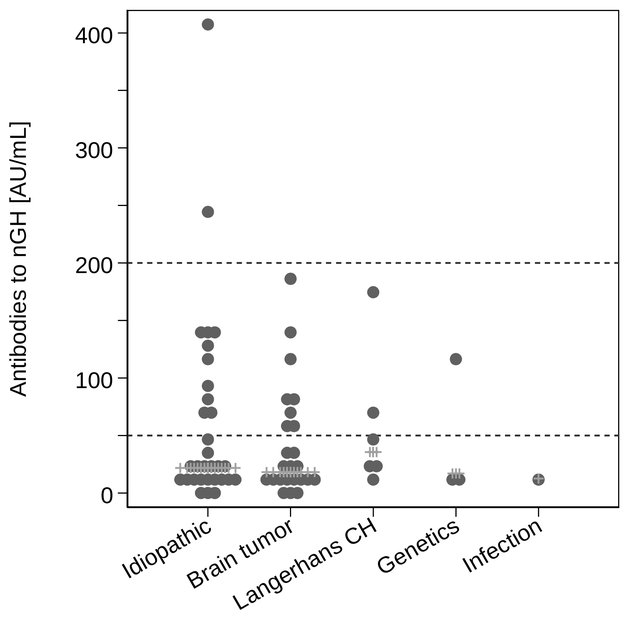


Fig. 1: Age at disease onset according to etiology

Fig. 2: n-GH antibody title according to etiology



RESULTS

Age at diagnosis is significantly associated with etiology; CDI occurs earlier in patients with genetic forms of CDI (p=0.009, fig. 1) and later in patients with brain tumor.

Autoantibody level in patient with different etiologies is shown in fig. 2.

Anterior pituitary hormone defects are more frequent in patients with LCH even before specific treatment began (p=0.008), while the association between anterior defects and tumors was significant only after treatment (surgery, radiation or chemotherapy, fig. 1).

Patients with normal pituitary stalk at disease onset were more likely to develop GH deficiency during follow up(p=0.043).

The median nGH antibody levels were overall similar in the 5 diagnostic categories, being in all cases <50 AU/mL. Interestingly, however, very high GH antibody levels(>200) were seen only in patients with idiopathic CDI (fig. 2). When sequential sera were available, GH antibodies decreased over time.

GH antibodies were higher in patients without pituitary stalk thickening (p=0.032), and did not differ according to gender, age at diagnosis, age at time of blood test, disease duration, treatment type, or anterior pituitary hormone defect.

		Genetic (N=5)	Idiopatic (N=32)	Brain tumor (N=49)	Langerhans Cell Histiocytosis (N=10)	P
TSH deficiency:	**Yes [n=23]**	0 (0%)	3 (9,4%)	14 (28,6%)	6 (60%)	0,005[a]
	No [n=73]	5 (100%)	29 (90,6%)	35 (71,4%)	4 (40%)	
ACTH deficiency:	**Yes [n=19]**	0 (0%)	3 (9,4%)	13 (26,5%)	3 (30%)	0,14[a]
	No [n=77]	5 (100%)	29 (90,6%)	36 (73,5%)	7 (70%)	
GHD:	**Yes [n=20]**	0 (0%)	9 (28,1%)	5 (10,2%)	6 (60%)	0,003[a]
	No [n=76]	5 (100%)	23 (71,9%)	44 (89,8%)	4 (40%)	

Tab 1: Hormonal defects in diagnostic categories

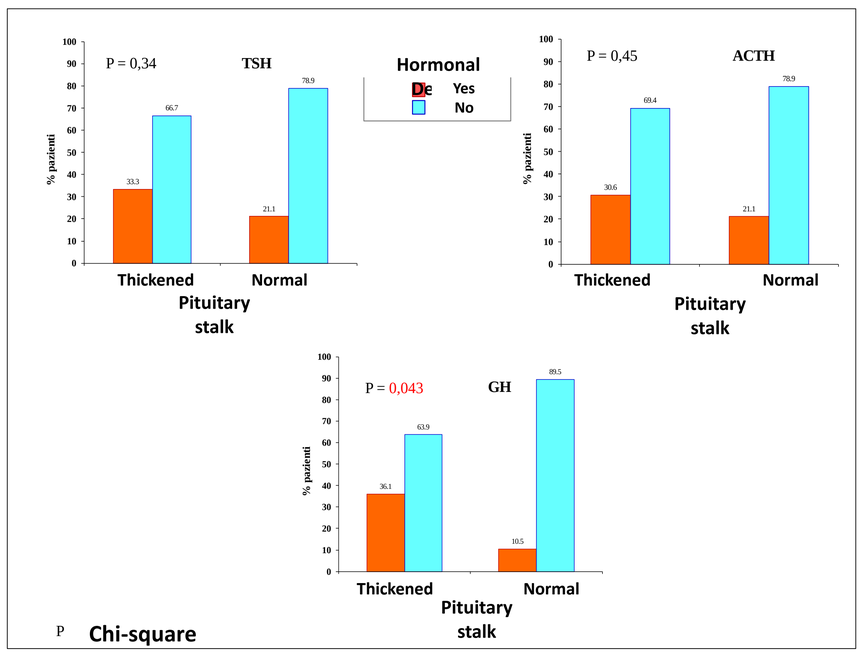


Fig. 3: Pituitary stalk thickness and pituitary hormone defects.

CONCLUSIONS

The study confirms the challenge of discovering new etiologic factors in idiopathic CDI, as well as identifying factors that predict a specific etiology. GH antibodies do not seem to associate with specific CDI etiologies, although the highest levels observed in the idiopathic form suggest autoimmunity as a possible contributor to the pathogenesis of this condition.

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