Primary Adrenal Insufficiency in children: results from a large nationwide cohort

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INTRODUCTION

Primary adrenal insufficiency (PAI) is a rare life-threatening disorder. Data on PAI in children are scanty, with the exception of Congenital Adrenal Hyperplasia (CAH) due to 21-hydroxylase deficiency (21OHD).

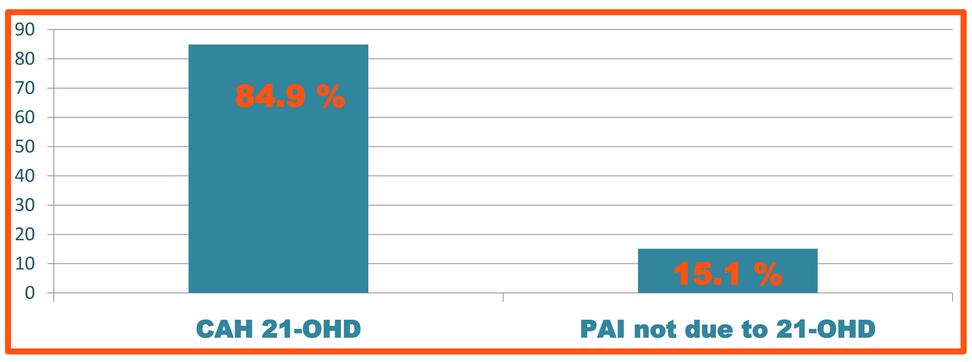
OBJECTIVE

The aim of this study was to evaluate the etiology of PAI in a large cohort of children and characterize the clinical presentation in subjects with PAI not due to 21-OHD.

METHODS

Children followed in 8 tertiary centers were retrospectively included. Data on signs/symptoms and laboratory findings at onset, time between onset and diagnosis and frequency of adrenal crisis, were collected.

Fig. 1 Percentage of PAI due to CAH 21-OHD vs not due to 21-OHD



Tab. 1 Baseline details of patients with not CAH 21-OHD PAI

N. of patients	121/803
M/F ratio	83/38
Age at onset (years)	6.7 ± 5.3
Age at diagnosis (years)	7.2 ± 5.5
Time between onset and diagnosis (months)	6.0 ± 12.9

Fig. 3 Time between onset of first sign/symptom and diagnosis of PAI

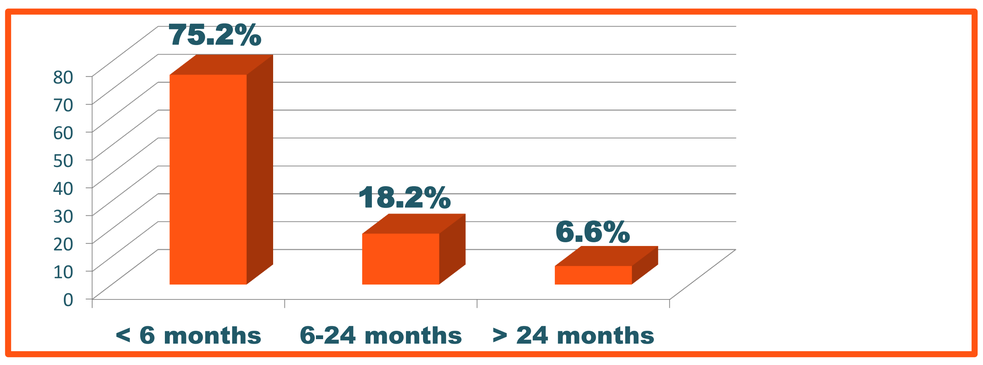
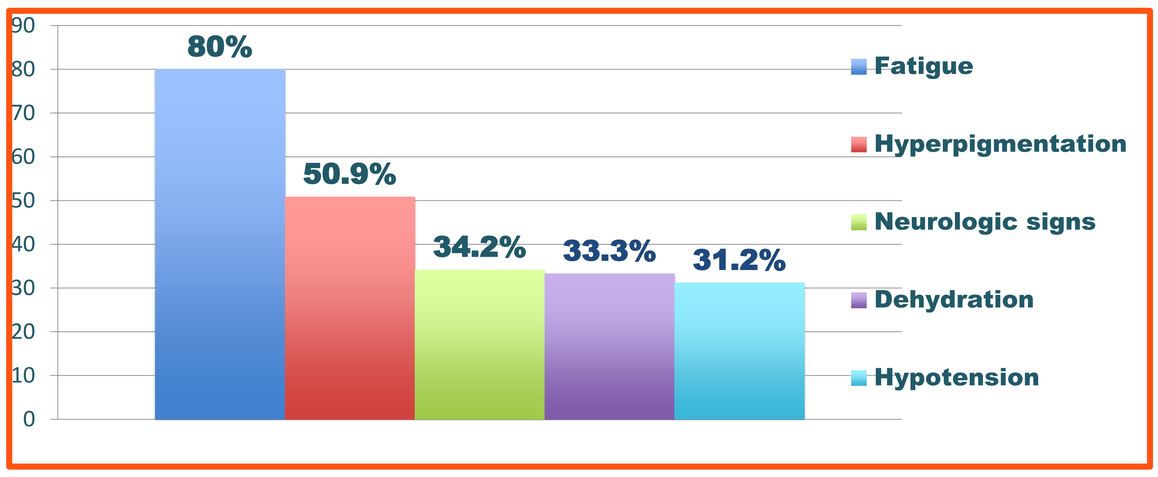


Fig. 4 Most common signs and symptoms in PAI children



RESULTS

Eight-hundred and three children were included in the study; 84.9% of patients (n=682) had 21-OHD CAH and were not reviewed further (Figure 1).
The etiologies of the remaining 15.1% (n=121) of children are summarized in Figure 2; 37.2% had autoimmune PAI (44.4% isolated; 55.6% polyendocrine syndromes); 25.6 % had steroid biosynthetic defects (DAX1 n=12; 17α-hydroxylase n=1; familial glucocorticoid deficiency n=5; 11β-hydroxylase n=3; 3β-hydroxysteroid dehydrogenase n=6; glycerol kinase deficiency n=2; other n=2); 20.7% had adrenoleukodystrophy; 6.6% had rare syndromes (Triple A, Pearson); 2 patients had infection and hemorrhage and in 10 no defined etiology was found.
Characteristics of subjects with PAI not due to 21-OHD are detailed in Table 1 and Figure 3.
Time between onset of first sign/symptom and time of diagnosis ranged from 0 to 78 months; in 91 (75.2%) patients, aged 5.9 ± 5.4 yrs, the diagnosis was performed in less than 6 months from the first sign/symptom (Figure 3).
The most common symptom at the onset of disease was fatigue; the others are reported in Figure 4. Furthermore, biochemical finding are detailed in Figure 5.
Overall mortality was <1% and severe adrenal crisis during a mean follow-up of 10 yrs were rare.

Fig. 2 PAI etiology not due to 21-OHD

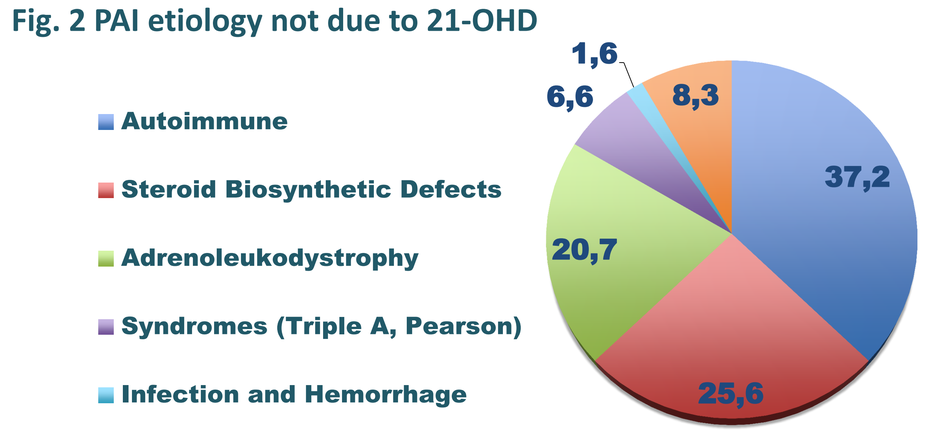
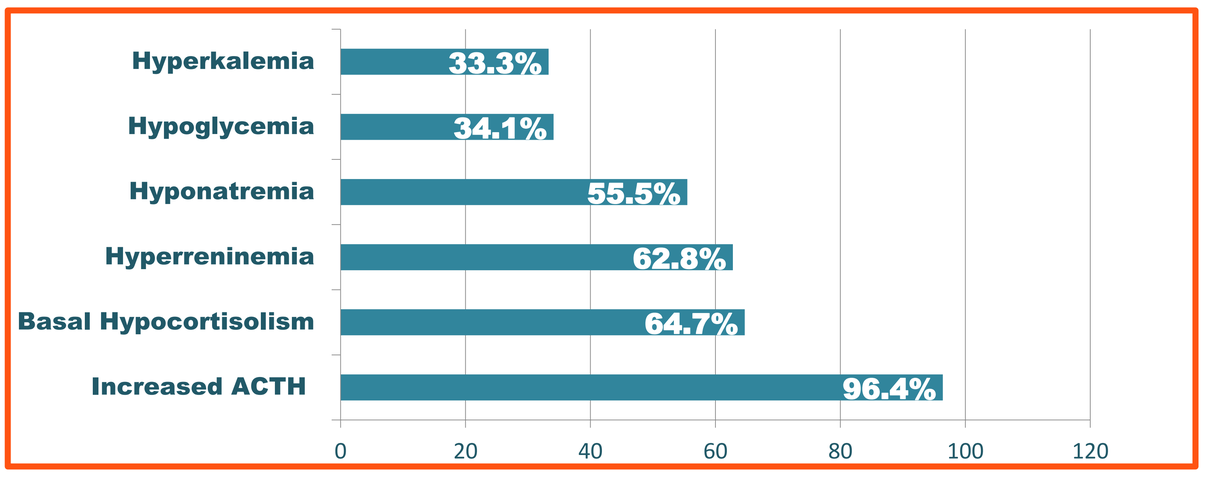


Fig. 5 Most common biochemical findings in PAI children



CONCLUSION

This large nationwide study document that the most common cause of PAI in childhood is 21-OHD CAH followed by autoimmunity, steroid biosynthetic defects and adrenoleukodystrophy. In non 21-OHD CAH subjects, symptoms at diagnosis are subtle and not specific, with the exception of hyperpigmentation; increased ACTH associated to hypocortisolism, hyperreninemia and hyponatremia are common, while hyperkalemia and hypoglycemia seems to be less frequent. Health outcome in our cohort is favorable with low mortality rate and low incidence of adrenal crisis during follow-up.

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55ESPE 34--P1
Adrenal
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DOI: 10.3252/pso.eu.55ESPE.2016
Poster presented at: ESPE 2016 PARIS 10-13 SEPTEMBER
PosterSessionOnline.com