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Are heterozygous carriers of CYP21A2 less vulnerable to psychological stress?

Conclusions

CYP21A2 carriers seemed to be less vulnerable to psychologically stressful events.

CYP21A2 carriers may have a survival advantage explaining the relatively high carrier rate.

Introduction

Congenital adrenal hyperplasia (CAH), due to 21-hydroxylase deficiency is one of the most common monogenic autosomal recessive disorders with an incidence of 1 in 15000. About 1 in 70 individuals in the population in Sweden are carriers of a classic CYP21A2 mutation.

It has been discussed whether heterozygotes have a survival advantage. The HPA axis has been reported to be more active in CYP21A2 carriers, possibly in response to a higher ACTH activity. The faster and more elevated cortisol response could enable a more rapid return to homeostasis. (Witchell et al 1997). On the other hand it has been hypothesized that the compensatory increase in CRH secretion could result in a vulnerability to anxiety and depression. Carriers have been shown to have lower 24 hour cortisol excretion but higher ACTH in response to CRH stimulation and psychometric assessment showed that these two factors predicted a predisposition to obsessive-compulsive behavior (Charmandari et al 2004).

Methods

371 parents of patients with classical CAH, SW or SV form, were identified through the Swedish CAH registry. Hence, carriers of a mutation associated with the classical forms of CAH were selected.

The birth or diagnosis of the child was used as the psychological stressor. Outcome measures were psychiatric diagnoses of the parents, in the national diagnosis registry, before and after the birth of a child with CAH.

Three control groups were used, and the parents were matched for sex and age: (i) parents of children in the general population, n=35607, (ii) children with diabetes type 1 (T1DM), n=35819, or (iii) children with hypospadias, n=13452.

Odds Ratio for the parents acquiring a psychiatric diagnosis after the birth or diagnosis of the child. Parents with a child with CAH compared to general population, child with T1DM, or hypospadias.

Compared with	Parents General population		Parents T1DM		Parents Hypospadias	
	OR	CI 95%	OR	CI 95%	OR	CI 95%
Psychiatric diagnosis						
Any psych diagnosis	0.6	0.4-0.9	0.6	0.4-0.9	0.6	0.4-1
suicide	0.4	0.1-1.1	0.3	0.1-1.2	0.3	0.1-1.1
psychosis	0.6	0.2-1.9	0.8	0.3-2.7	0.9	0.3-2.9
mood	0.5	0.3-1	0.5	0.3-1	0.4	0.2-0.9
anxiety	0.8	0.4-1.5	0.6	0.3-1.1	0.6	0.4-1.2
Substance misuse	0.5	0.3-1.1	0.2	0.1-0.7	0.3	0.1-0.7
Alcohol misuse	0.5	0.3-1.2	0.3	0.1-0.8	0.3	0.1-0.9
stress	0.3	0.1-0.8	0.3	0.1-0.9	0.3	0.1-1.1

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CAH and T1DM are both potentially life threatening diseases that requires daily treatment. Hypospadias and CAH affect genital development and may lead to uncertainty of gender assignment at birth. All these situations are known as stressful events for the parents.

Results

Parents of children with CAH had less risk of receiving any psychiatric diagnosis of affective disorder or substance misuse after the diagnosis of the child, compared to all three control groups:

- (i) parents in the general population,
- (ii) parents with a child with hypospadias
- (iii) parents with a child with T1DM respectively

Parents of children with CAH were also less likely to receive a diagnosis of affective disorder than parents of healthy children and parents of children with hypospadias or T1DM. In addition, substance misuse was less likely compared to parents of children with diabetes or hypospadias and stress compared to parents of children with T1DM or of general population.

There was no difference in psychiatric morbidity prior to the child birth between the evaluated groups.

References

Witchell et al JCEM 82:2097-2101, 1997
Charmandari et al JCEM 89:2228-2236, 2004

Discussion

The aim of the study was to investigate the vulnerability to psychological stress in obligate CYP21A2 carriers. An increased activity in the HPA axis could be an advantage in stressful situations. At the same time a compensatory increase in CRH could result in increased vulnerability to anxiety and depression.

Our findings indicate that carriers were less vulnerable to psychologically stressful situations, assessed as the likelihood of receiving a psychiatric diagnosis of mood disorder, anxiety or substance misuse.

