Journée Association Surrénales

Hyperplasies Congénitales des Surrénales

Programme et résumés des communications

Program and Abstracts

association surrénales

Vendredi 5 avril 2013 Paris

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• **8h30-9h00 : Accueil des participants**

9h00-9h15 - Introduction
Association Surrénales
et Président du Conseil Scientifique

A – Diagnostic
Modérateurs : *Pr Juliane Léger*
et Pr Sophie Christin-Maître

9h15-10h00 : Corrélations phénotype-génotype des HCS
Pr Yves Morel,
Dr Christine Bellané-Chantelot,
Pr Michel Polak

10h00-10h30 : Les outils du diagnostic anténatal
Dr Véronique Tardy

10h30-11h00 : Impact du traitement anténatal par DXM
Dr Svetlana Lajic

11h00-11h20 : L'usage des bases du dépistage néonatal
Pr Jean Claude Carel

• **11h20-11h45 : Pause café**

B - Clinique
Modérateurs : *Pr Pierre Châtelain*
et Dr Laurence Guignat

11h45-12h15 : Comment optimiser la croissance des enfants HCS
Dr Patricia Bretonès

12h15-12h45 : Inclusions surrénaliennes : équilibre thérapeutique ou facteur développemental
Dr Hedi L. Claahsen-van der Grinten

12h45-13h15 : Fertilité des hommes HCS
Dr Claire Bouvattier et Pr Jacques Young

• **13h15-14h15 : Déjeuner**

14h15-14h45 : Fertilité et sexualité femmes HCS : formes précoces et tardives
Dr Maud Bidet et Dr Lise Duranteau

14h45-15h15 : Conséquences HCS : cœur, os et métabolisme
Dr Anne Bachelot

C - Traitement
Modérateurs : *Dr Sylvie Cabrol*
et Pr Philippe Chanson

15h15-15h45 : Chirurgie réparatrice filles HCS : pratiques et expérience française
Pr Pierre Mouriquand

15h45-16h00 : La chirurgie féminisante dans l'hyperplasie congénitale des surrénales en France
Dr Thomas Blanc

• **16h00-16h25 : Pause café**

16h25-16h55 : Facteurs prédictifs de l'équilibre thérapeutique
Pr Philippe Touraine

16h55-17h25 : Nouveautés thérapeutiques
Pr Richard Ross

17h25-17h45 : L'éducation thérapeutique a-t-elle une place dans le traitement des HCS
Madame Sabine Malivoir

17h45-18h00 : Conclusions et Synthèse
Pr Jérôme Bertherat et Dr Delphine Zenaty

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21-HYDROXYLASE DEFICIENCY (21OHD): Relationship between genotype and phenotype.

Yves Morel[1], Véronique Tardy[1], Rita Menassa[1], Ingrid Plotton[1], Pierre Chatelain[2] and Claire Lise Gay[2] and the French 21-hydroxylase Consortium.

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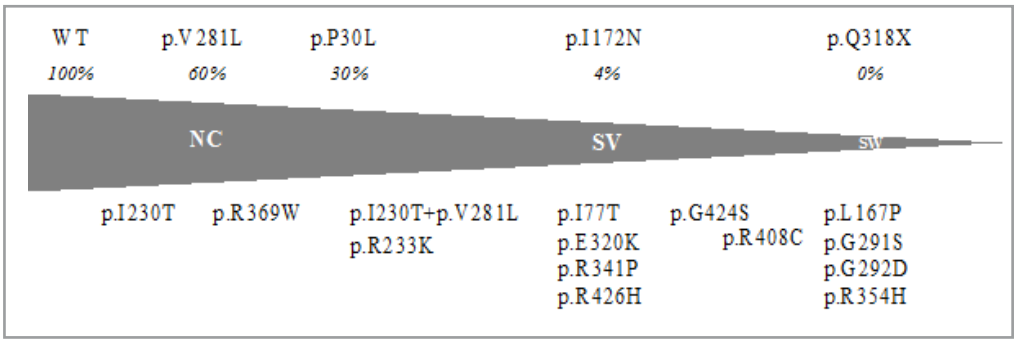
Steroid 21OHD is the most frequent cause of congenital hyperplasia and a genetic autosomal recessive disorder. In most populations, classical forms occurs in approximately 1 in 14.000 live births and is constituted by the salt wasting (SW) and the simple virilizing forms (SV). Both include female external genitalia virilization by fetal adrenal androgen hyperproduction and severely impaired glucocorticoid and mineralocorticoid secretion. In the non classical (NC) form, mineralocorticoid secretion is conserved and female "in utero" virilization absent; phenotypic manifestations due to androgen excess are variable even absent, occurring either in childhood later than in the SV, or in adult women referred for hirsutism, menstrual irregularity and decreased fertility. Men are often asymptomatic, underlying the difficulty to evaluate the incidence of this mild form of CAH.

The active gene, CYP21A2, and the pseudogene, CYP21PA1 are located in the HLA class III and duplicated in tandem with C4 and Tenascin genes. A highly nucleotide homology between the duplicated region encompassing these 3 genes indicates frequent crossover events, making genetic distinction of the loci difficult. In most populations, classical CAH occurs in approximately 1 in 14.000 live births (3) and is constituted by the simple virilizing (SV) and the salt wasting (SW) forms. Both include female external genitalia virilization by fetal adrenal androgen hyperproduction and severely impaired glucocorticoid and mineralocorticoid secretion

Genotype : Today, around 130 lesions of the CYP21A2 gene are reported (http://www.imm.ki.se/CYPalleles/cyp21.htm). Since 1988 to 2010, we have determined the genotype of about 3200 patients with 21OHD. By complete sequencing and MLPA, genetic lesions have been determined in almost all families 99.8%. The most common mutations are IV2-13A/C>G in SW and I172N in SV. Nevertheless, two mutations were prevalent in some ethnic groups: the one in Reunion Island, the other Q318X in North Africa. The 7 most frequent pseudogene derived lesions (mutations or large rearrangements) representing 85% of the 21OHD alleles, each one occurring with a frequency superior to 3%. In our cohort, their incidence is in classical (SW + SV) : IVS2-13A/C>G (30%), large rearrangements (25%), p.I172N (17%), p.Q318X (7%) and in non classical forms: p.V281L (55%), IVS2-13A/C>G (9%), large rearrangements (8%), p.I172N (4%) and p.Q318X (3%). Mutations are divided into three groups according to residual enzyme activity, depending on the nature of the mutations and in vitro studies in case of missense. The first group consists of mutations abolishing enzyme activity and thus associated with SW disease, as large rearrangements, nonsense, frameshift or missense mutations. The second group, found in patients with SV, consists mainly of the missense p.I172N; residual 21-hydroxylase activity is very low but sufficient to prevent from neonatal salt-wasting. The third group includes mutations such as p.V281L and p.P453S that produce enzymes retaining 20 to 70% of normal activity, and are associated with NC. Rare mutations (frequency< 1%) were detected on almost 340/ 6 400 CAH alleles (6%).



Correlation genotype-phenotype : The less severely mutated allele determines the phenotype. Phenotypic expression reflects not only the enzymatic defect but also the steroid metabolism and action. A very good correlation between genotype and phenotype exists whether the criteria is the degree of residual 21-hydroxylase activity: Salt wasting vs null/null genotype to slightly increase of 17OHP (>36 nmol/L or 12 ng/ml) after ACTH stimulation vs mild/mild (V281L/V281L) genotype. Usually, the classic forms (SW + SV) could be easily distinguished from the non classic form. The onset of symptoms in SV forms appears before 5 years of life. Nevertheless, the degree of virilization could be variable due to individual factors resulting for variable steroid metabolism and action. Some girls with genotype (I172N/I172N or severe mutations) present a degree of salt loss without virilization of external genitalia. Although careful molecular study resolved almost all discrepancies i.e. gene conversions associated with non classic form (NC), V281L always associated with other mutations in SW, P30L alone or associated with a gene conversion, some exceptions have been reported.

Conclusion : 21OHD genotyping appears essential for a new approach of genetic counseling, prenatal diagnosis, prediction of clinical form after postnatal screening, helpful for treatment management and to define the post-ACTH 17OHP values indicating the borders between NC, heterozygote and normal subjects.

Notes

Importance of molecular diagnosis in at risk relatives, in partners of patients with congenital adrenal hyperplasia (CAH) and carriers of classic CAH alleles.

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Congenital Adrenal Hyperplasia (CAH) due to 21-hydroxylase deficiency is one of the most common inborn endocrine disorders and is inherited as an autosomal recessive disorder. Loss-of-function mutations in the 21-hydroxylase (CYP21A2) gene account for approximately 95% of cases. Besides the classic form characterized by a complete or near-complete loss of enzyme activity, which leads to salt-wasting or simple virilizing CAH generally revealed at birth, there exists the nonclassic form (NC-CAH) due to partial enzymatic defect, with late-onset symptoms and diagnosis in childhood, after puberty or in adults. The classic forms of CAH occur in a frequency of approximately 1 in 15,000 in the general population whereas the NC-CAH is more frequent with an estimated incidence of about 1 in 1000. Prevalence could be much higher in some ethnic groups.

On the basis of neonatal screening programs, the incidence of carriers is estimated to 1:60. Consequently, a patient with classic CAH would have a 1 in 120 probability of having a child with classic CAH. For NC-CAH, about two thirds of patients are compound heterozygotes, carrying one allele that causes classic CAH and one that causes NC-CAH. The milder mutation determining the phenotype, the NC-CAH parent has a risk of 1 in 240 of having a child with classic CAH. However, at least two studies, one on the analysis of children of NC-CAH women (Moran et al, JCEM, 2006), and the second on partners of NC-CAH women (Bidet et al, JCEM, 2009) suggested a much higher risk for offspring to have CAH (2.5% of classic CAH for Moran study). Such an assumption is corroborated by recent studies suggesting a carrier frequency of 15% in a Spanish (Parajes et al, Plos One, 2008) and of 10% in a middle European (Baumgartner-Parzer et al, JCEM, 2004) population, both being clearly higher than that deduced from newborn screening programs.

The second issue in familial screening is the molecular diagnosis of at risk relatives even in the absence of symptoms suggesting 21-hydroxylase deficiency. First, the NC-CAH has a variable clinical expression for the same CYP21A2 genotype and even within a family. Thus, Bidet and Coll. (Bidet et al, JCEM, 2009) found that among 30 siblings (including 16 sisters) who were homozygotes or compound heterozygotes for CYP21A2, 11 were asymptomatic. Second, heterozygote subjects carrying CAH alleles cannot be reliably discriminated from those carrying NC-CAH alleles by post-ACTH plasma 17-hydroxyprogesterone (17OHP) and 21-deoxycortisol (21DF). Finally, cut-off values of post-ACTH 17OHP and 21DF for normal subjects and heterozygotes remain controversial and dependent on laboratory normal values.

In conclusion, the high frequency of heterozygotes in the general population, the fact that hormonal dosages cannot reliably detect heterozygous subjects with classic CAH allele and that two-third of NC-CAH have one allele associated with classic CAH warrant the CYP21A2 molecular diagnosis in partners of patients with CAH, of carriers of classic CAH alleles and in at risk relatives. This is of utmost importance to offer an appropriate genetic counselling.

Notes

Insufficient response of cortisol to stimulation in four patients with non classical congenital adrenal hyperplasia: exceptions of genotype-phenotype correlation ?

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Background : nonclassical congenital adrenal hyperplasia (NCCAH) presents during childhood, adolescence or even adulthood with various degrees of hyperandrogenism1-7. Diagnosis is established through a stimulation Synacthen® test and further genotyping1-7. Cortisol insufficiency is generally not a feature of NCCAH2-6, and cases with such deficiency7-8 have not been the focus of a careful description.

Aims : to present some cases of NCCAH by mutation of the CYP21A2 gene, in which impaired cortisol secretion was documented by using a Synacthen® stimulation test.

Method: we describe 4 patients followed during childhood in the Service d'Endocrinologie Pédiatrique, Hôpital Necker Enfants Malades, who were diagnosed as having NCCAH with documented CYP21A2 mutation and who presented with subnormal cortisol response in Synacthen® test (<18 µg/dl) and/or high levels of basal ACTH.

Results : 3 girls and a boy (mean age: 12,5 years, range: 8,3-17,3) displayed a subnormal cortisol peak after ACTH stimulation (mean: 14,0 µg/dl, range: 11,6-18,3) and/or a high ACTH basal level (mean: 106,7 ng/l, range: 39-160). 3 of them were near end of puberty. Fatigue was reported in two cases, which improved after treatment with hydrocortisone. No severe acute episodes have been noted.

Conclusion : some patients with NCCAH have an impaired cortisol production, which has already been reported in the litterature7-10. The clinical impact and risk of developing cortisol insufficiency has not yet been fully established, as accidents in patients with NCCAH are scarcely reported8. Our patients did not report severe episodes. It is difficult to propose strict guidelines concerning the need of glucocorticoid replacement in patients with NCCAH2,9-10. Nevertheless, we suggest initiation of glucocorticoid treatment in those who display a diminished cortisol peak in Synacthen® test or have a high basal ACTH level, when under stressful conditions, and to double or triple the dose in patients who are already treated.

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Notes

New strategy of management of pregnancies at risk of 21-hydroxylase or 11-hydroxylase deficiency using fetal sex determination in maternal serum; French experience 2002-2011

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Prenatal treatment by dexamethasone (DEX) is proposed since 1980 to prevent genital virilization in girls affected with classical form of 21 or 11-hydroxylase deficiency. DEX efficiency depends on term of start, posology and preservation until delivery in case of affected girl. As DEX remains controversial regarding possible side effects on treated fetuses, we report the French experience based on fetal sex determination in maternal serum (SRY test) to avoid treatment of males. The following protocol was proposed since 2002: early datation of gestation by ultrasonography, SRY test between 4 and 5.5 weeks of gestation (WG) with aim to start DEX before 6 WG if negative; confirmation of early negative tests at 8 WG and prenatal diagnosis on chorionic villi. In case of positive SRY test, a prenatal diagnosis by amniotic fluid or a management at birth was discussed. There were **258 fetuses** with SRY test, **134 males** and **124 females**. Delay of menstruations was inaccurate for datation in 20 % of cases, underlying the necessity of ultrasonography. Sensitivity of an early SRY test was confirmed by karyotype and at birth but it has to be performed after 4 WG to avoid false-negative cases. Positive SRY test prevented treatment for 90 males, realized before 5.4 WG for 78; for the 44 in utero treated males, the positive test allowed to stop DEX. Prenatal diagnosis was realized for only 39 males. Regarding females, 17 were affected with 21 or 11-hydroxylase deficiency, all prenatally diagnosed. DEX was efficient for 12 girls, started at the latest at 6.4 WG. DEX was inefficient for 5 girls, 3 presented with moderate posterior labial fusion but no clitoromegaly (DEX start at 4.3, 6.4 and 7 WG) and 2 with a severe virilization Prader Stage 3 to 5 (DEX start at 8.3 and 13 WG). There were several explanations for partial efficiency: start after 6 WG, bad maternal compliance, possible error in datation, DEX maternal metabolism. Maternal tolerance was correct on the condition to respect low calorie and poor salt diet; bad side effects were described for 2 mothers in a particular context: gestational diabetes and arteriel hypertension in an obese woman, temporary acute pancreatitis in a woman with previous cholecystectomy. The in utero treated children didn't present any malformation at birth and mensurations were correct.

Thus, SRY test is usefull to avoid DEX in males; respect of this protocol, in particular DEX efficiency in preventing virilization in girls, implies a very closed collaboration between clinicians and biologists. Multicentric retrospective and prospective studies of treated children and mothers will be essential to precise DEX safety. These studies will take place in France to contribute to international recommendations for prenatal management of 21- and 11OHD.

Notes

Prenatal Dexamethasone Treatment of Children at Risk for Congenital Adrenal Hyperplasia: The Swedish Experience and Stand-point

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The most common form of CAH, 21-Hydroxylase deficiency, results in virilisation of external genitalia in severely affected female fetuses. Prenatal treatment of CAH with dexamethasone (DEX) has been administered since the mid-1980s and is effective in reducing virilisation in CAH-affected girls. The treatment has to be initiated early in pregnancy, before prenatal testing is possible. Consequently, seven out of eight fetuses (all boys and CAH-unaffected girls) are treated in early pregnancy without any benefit of the treatment per se, until prenatal testing can determine the sex and diagnostic status at the end of the first trimester. CAH-affected girls are treated until term.

Results from animal studies, as well as studies on prenatal glucocorticoid therapy in other contexts, have raised concerns regarding possible negative effects on behavioural and somatic development in treated children. The prenatal treatment of CAH is considered to be safe in the short-term perspective, while there still are few long-term follow-up studies. In Sweden, prenatal treatment of CAH has been administered within the frameworks of a clinical study since 1999. We have also conducted retrospective follow-up studies of mothers and children treated in Sweden during 1985 – 1995 . In summary, maternal side-effects were such that can be expected with glucocorticoid/DEX treatment. Most of the maternal side-effects seem to disappear after discontinuation of treatment, but in our experience, approximately 50% of the mothers treated during pregnancy, and all mothers treated until term reported some type of discomfort that could be attributed to DEX. In general, treated children were born at term and were not SGA. As a group, they did not exhibit teratogenous effects/gross malformations, although eight severe adverse events were noted in the treated group, compared to one in the control group. In the follow-up studies on behavioural development parent reports indicated good general adaptation, psychological well-being, and school performance in DEX-exposed children as compared to non-treated controls. Direct neuropsychological assessments of the children showed normal results on measures of IQ, learning, and memory. However, an adverse effect was observed in the form of impaired verbal working memory in CAH-unaffected short-term treated cases. The verbal working memory capacity correlated with the children´s self-perception of difficulties in scholastic ability, another measure showing significantly lower results in CAH-unaffected, DEX-exposed children. These children also reported increased social anxiety. In the studies on gender role behaviour, we found indications of more neutral behaviours in DEX-exposed boys. The small sample size and the retrospective study design limited the conclusiveness of the results but nevertheless, the results cause concern, as no side-effects should be tolerated in CAH-unaffected children who do not benefit from the treatment

per se. In a Polish follow-up of dexamethasone treated CAH girls, contradictory results was seen, with better results overall in Dex treated CAH girls compared to untreated CAH sisters but poorer results of visual perception, analysis of spatial material and visual memory task in short-term Dex treated healthy girls compared to untreated CAH girls and long-term treated CAH girls . Further support for negative Dex effects also emerge from later American studies where Dex treated CAH girls have a slower mental processing than controls on several neuropsychological variables .

As a consequence of our findings of possible adverse effects further treatment of patients has been put on hold in Sweden pending additional studies. Multi-source assessment methods should be applied, including both direct assessment of the treated individuals and collateral information from parents and possibly teachers. Moreover, the assessment should focus on both behavioural - including cognitive - and somatic outcomes. In this way our findings can be either confirmed or challenged and we will eventually be able to conclude whether prenatal DEX treatment has a role or not in the clinical management of CAH.

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Notes

Efficiency of neonatal screening for congenital adrenal hyperplasia due to 21-hydroxylase deficiency in children born in mainland France between 1996 and 2003

Bénédicte Coulm[1], Joel Coste[1], Véronique Tardy[2], Emmanuel Ecosse[1], Michel Roussey[3], Yves Morel[2], Jean-Claude Carel[4], on behalf of the DHCSF study group.

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Neonatal screening for congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21OHD) is mainly intended to prevent death due to salt wasting but remains controversial, because of the number of false-positive results and the ease with which most female cases can be identified by virilised genitalia at birth. The aim of this study was to assess the efficiency of the national screening programme for 21OHD.

This was a population-based study based on the French national neonatal screening program, using data provided by paediatric endocrinologists nationwide and reference centre for genotyping. All newborns screened for 21OHD in mainland France between January 1st, 1996 and December 31st 2003 were included. Screening efficiency indicators, disease severity and contribution of screening to early diagnosis, disease-specific mortality before and during the study period were evaluated.

6,012,798 newborns were screened, 15,407 were considered positive for 21OHD and 383 cases were identified, giving a prevalence of 1/15,699 births. The positive predictive value of screening was 2.3% (95% CI, 2.1-2.6), with a sensitivity of 93.5% (90.9-95.9) and a specificity of 99.7%. The false-positive rate was particularly high in preterm infants, for which the positive predictive value was 0.4% (0.2-0.5). Screening allowed clinical diagnosis in 162 of 383 cases (42%), the others being detected clinically or through family history. There was a trend towards declining neonatal mortality due to 21OHD.

Conclusion. In this large, population-based study, the efficiency of routine 21OHD screening was moderate in neonates born at term and very low in preterm neonates. We recommend the discontinuation of screening, as currently performed in France, in preterm newborns.

Notes

Growth from birth to adulthood in Congenital Adrenal Hyperplasia (CAH): Data from the French Opale Cohort.

Patricia Bretones[1], Benjamin Riche[2,5], Catherine Cornu[3,5], Emmanuel Pichot[1], Véronique Tardy[4,5], Yves Morel[4,5], Pierre Chatelain[1,5], Marc Nicolino[1,5], Michel David[1,5] in the name of the Opale study investigators.

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Despite management improvement of Congenital Adrenal Hyperplasia (CAH), short adult stature is still often encountered. The data presented were generated by a French multicentre retrospective study named Opale. The main objective was to build a model for predicting adult height in CAH-children. The Opale cohort included children born between 1970 and 1991, diagnosed for CAH and followed to adult height by specialized paediatric centres. Patients were excluded when CAH was associated with chronic disease or treatment such as GH or anti-inflammatory corticoid. Based on centralized genotyping, CAH patients with 21-Hydroxylase (21-OH) gene defect were classified in salt wasting (SW), simple virilizing (SV) or non classical (NC) form. Clinical characteristics, auxological and treatment data were collected from individual patient's file. X-rays for Bone Age (BA) were all re-evaluated by a single expert. Gender-related growth charts were built using the LMS (Box-Cox Cole and Green) method and exact measurement of age. A multivariate analysis was led to identify parameters associated to short adult stature. A mixed linear regression based on maximum likelihood method was used to develop a model of bone maturation taking into consideration gender, genotype and age at treatment initiation.

Five hundred and eleven CAH-patients were enrolled in 30 centres, including 21-OH (n=496) 11-beta-Hydroxylase (n=12) and 3-ß-OL-Dehydrogenase (n=3) gene defect respectively. 21-OH CAH split into 284 SW (118 boys, 166 girls), 127 SV (68 boys, 59 girls) and 100 NC (28 boys, 72 girls). All but 8 NC-patients received HydrocortisoneR. Growth charts according to gender and genotype were generated from these 21-OH CAH, showing that mean childhood's heights were close to those of normal French population. In contrast observed mean adult height was -1.1 SDS, pointing to a marked reduction in pubertal growth spurt. Excessive bone maturation was observed reaching at the age of 8 years an apparent maximum advance of 2 years in boys and 1.5 year in girls respectively. Multivariate analysis showed an association between short adult height (SDS < -2) and mid-parental height, genotype, height at the age of 8 and Tanner stage 2 at 8 years. Interestingly at a chronological age of 8 years, the association between advanced BA and short adult height is strong with an OR= 3.2 for one advanced BA-year. No correlation was observed between mean HydrocortisoneR posology at different ages and short adult height.

In summary data from the French 21-OH CAH Opale cohort generate growth curves from birth to adulthood for boys or girls presenting with the main three genotypes. As currently managed the 21-OH CAH Opale cohort shows excessive bone maturation during the first 8 years, reduced pubertal spurt and loss in adult height close to -1.1 SD. A model predicting adult height at 8 years is established. These data point to the medical need for treatment improvement aiming at 1/ preventing excessive bone maturation during the first 8 years and 2/ optimizing pubertal spurt, in order to narrow down the difference between current decreased adult height and target height.

Acknowledgment: We express our gratitude to all patients and their parents as well as to all investigators involved in the Opale Study. The Opale study was supported by "The Association Surrénales" Scientific Council generous grant and by PHRC interregional 2008 grant.

Notes

Testicular Adrenal Rest Tumors in congenital adrenal hyperplasia (CAH) – a developmental factor or a therapeutic disequilibrium?

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Infertility is a serious and common problem in female as well in male CAH patients. The most important cause of male infertility in CAH patients is the presence of testicular adrenal rest tumors (TART). The reported prevalence in adult CAH patients is up to 96%. TART have no malignant features but because of their typical central localization near the mediastinum testis, compression of the seminiferous tubules by progressively growing and longstanding tumors may finally lead to obstructive azoospermia and irreversible damage of the surrounding testicular tissue. TART contain adrenal specific enzymes and ACTH receptors and produce adrenal specific hormones suggesting that these tumors arise from adrenal–like cells. Therefore, it is thought that elevated ACTH levels as in poor hormonal control contribute to tumor growth. However, as TART is also present in well controlled patients, other unknown factors may play a role in the pathogenesis of TART. TART is already present in childhood with an increase in prevalence from the age of 10 years old. However, the prevalence in younger children is probably underestimated because very small adrenal rests may not be detected.

Treatment options of TART are still controversial. In some patients, intensifying glucocorticoid therapy may lead to reduction of the tumor size most likely due to suppression of ACTH secretion thereby improving testicular function. During puberty high dosages of glucocorticoids may have a negative effect on pubertal growth with consequently reduced final height. Therefore, the balance between different treatment goals during puberty can be difficult. Testis sparing surgery may be considered for relief of pain and discomfort. However, it is controversial whether testis-sparing surgery can also improve gonadal function and whether it can be performed without causing additional gonadal damage. Cryopreservation is recommended as soon as possible in CAH patients with TART since actually no reliable fertility prognosis can be given.

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Notes

Sexuality, fertility and gonadotropic axis evaluation in 191 men born with classic 21 hydroxylase deficiency (21OHD) : first results of a French multicentric survey.

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Context : Since almost 10 years an increasing number of publications indicate that fertility in males born with congenital adrenal hyperplasia (CAH) due to 21OHD is far from normal, as initially thought, but in fact severely impaired in most of them. The occurrence of testicular adrenal rest tumors (TART) is considered to be the main reason for fertility impairment. However, to date sexual life and its hormonal determiners were not evaluated in CAH/21OHD adult patients.

Aims : To create a French network in order to study the consequences of the disease on sexual life, fertility and on testicular functions and gonadotropic axis in post-pubertal men born with CAH/21OHD as well as the quality of medical care.

Methods : Implementation of an active network of teaching and general hospitals and of liberal endocrinologists in France. Data analysis from medical files collected in each center and patients' responses to two questionnaires concerning personal life and sexual life (GRISS). Evaluation of their correlation to clinical, morphological (testes) and hormonal relevant data collected from these files to specify the influence of testicular and gonadotropic dysfunctions as well as the therapeutical compliance.

Results : After 18 months, 191 patients with a median age 28 ± 9 years (18-50), have been already included in the study from 28 different teams. From the 191 men, 73% have a salt-wasting (SW) and 27% pure virilizing forms (SV). Their mean height (mean±SD) was 167±8 m and the BMI 26±5 Kg/m2. On average, all the patients received: 2.6 ± 1.3 hydrocortisone 10 mg Tablets and SW patients received also 1.8 ± 1.5 fludrocortisone 50µg Tablets. From the 133 CAH/21OHD patients who underwent testicular ultrasound, 43 (32%) had TART. Surprisingly, a sperm count was only performed in 54 (28%) of them. From these 54, 40 (74%) had abnormal sperm count (azoospermia: 11%; oligospermia and/or altered mobility and/or altered morphology: 63%). Hormonal evaluation of the testicular functions and the gonadotropic axis will be discussed. A partial evaluation of couple life in February 2013 showed that 68/100 (68%) patients were living with a female partner and that 28 out of 68 (41%) had children.

Conclusions : At the end of this program, a specific map of centers taking care of CAH/21OHD men in France will be available. Genotype-phenotype relationship and it influence on personal life, sexuality and fertility will be established in a significant series of men suffering the disease. Recovery the remaining questionnaires, expanding the network to non- academic and liberal Endocrine teams are the main currently tasks of the network to optimize completeness and representativeness of the patient sample. Thanks to this network an educational program will be implemented to explain the gaps detected and to improve the care of these patients in the field of fertility and sexuality.

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Notes

Sexual function outcome and fertility in women with Congenital Adrenal Hyperplasia (CAH)

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Genital masculinization of affected newborn girls with CAH can be of variable degree. Feminizing genital surgery comprises clitoroplasty and vaginoplasty with additional labioplasty if required. The surgery is commonly performed in early infancy for cosmetic reasons and for the psychological benefit of the child's genital appearance for the parents and the family. However 1) evidence for this hypothesis is lacking 2) most studies which have assessed the long term outcome of girls who had early genital surgery raise concerns on surgery complications that may impact on sexual function, sexual behavior and fertility 3) some adult patients and support groups ask for patient involvement in the decision-making procedure relative to surgery.

Long term outcome data of early genital surgery in women with CAH are limited but we and others have shown that vaginal stenosis, pain, reduced clitoral sensibility and low score of satisfaction are frequent (, ,). In addition, poorer long term psychosexual outcome may be observed regardless of surgery. There is currently no consensus about the timing and type of surgery for when and how feminizing surgery should be performed. Until then 1) decisions about surgery in CAH girls will benefit from discussions within a multidisciplinary team and the surgical procedure performed only by a specialist 2) studies that rigorously compare surgical results and sexual and psychological outcome of patients early operated are needed.

Reduced fertility has been commonly reported in patients with classical CAH. The earliest studies reported a pregnancy rate of 0-10% in women with the salt wasting form and 33-50% in simple virilizing form. Some recent studies are more optimistic and a recent study has presented the pregnancy rate as the proportion of women trying to conceive and reported a near normal conception rate for women with classical CAH (4). Hypofertility has been reported to several causes: post-surgical difficulties in intercourse, psychological factors, androgen and progesterone oversecretion, anovulation and menstrual irregularities. A recent study evaluated LH pulsatility in CAH patients and reported a LH pulsatility normal in CAH women well controlled by hormonal treatment, unlike undertreatment is responsible for hypogonadotropic hypogonadism (5). These study confirm that optimized glucocorticoid and mineralocorticoid regimes during fertility monitoring should be an important concern in CAH women, in particular suppression progesterone concentrations during the follicular phase. In non classical CAH women, subfertility is relative and glucocorticoid treatment should be prescribed to normalize menstrual cycles and/or reduce incidence of miscarriages (6).

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Notes

Adult consequences of congenital adrenal hyperplasia

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Improvement of CAH diagnosis and treatment in childhood has raised the question of adult health and care. In adulthood, the aims of the medical treatment are to substitute steroid deficiency but also to avoid the long-term consequences of glucocorticoid use. In such an intervention, there is a narrow therapeutic window through which the intended results can be achieved. Osteoporosis has been an understandable concern for adult patients with CAH who may receive or have received supraphysiological doses of glucocorticoids. Some previous reports on bone mineral density (BMD) in adult CAH patients showed no significant differences in BMD between patients with CAH and controls, but others have found lower BMD in all or some subpopulations of CAH patients. These reports differ with respect to age selections and glucocorticoid regimens. In reports documenting the BMD reduction, this outcome has been attributed to an accumulated effect of prolonged exposure to excess glucocorticoids during infancy and childhood. We recently conducted a trial to establish the role of the total cumulative glucocorticoid dose on BMD. We demonstrated that there was a negative relationship between total cumulative glucocorticoid dose and lumbar and femoral BMD. In this study, we showed the benefit from the preserving effect of estrogens in women compared to men. BMI also appeared to protect patients from bone loss. Patients with CAH also commonly have risk factors for cardiovascular disease including obesity, hypertension, and insulin resistance. Some studies of CAH support the contribution of glucocorticoid therapy to the development of obesity. Measurement of body composition using DXA has also demonstrated increased fat mass in young adults with CAH. These findings are potential indicators for increased cardiovascular risk in CAH patients.

In light of this, physicians should bear in mind the potential consequences of glucocorticoids on bone and metabolism and therefore adjust the treatment and improve clinical and biological surveillance from infancy. Furthermore, specific preventive measures should be discussed right from the beginning of glucocorticoid therapy. Finally, it highlights the importance of long term follow up of these patients and of transitional care between childhoods to adult life.

Notes

Chirurgie de reconstruction chez la fille porteuse d'une Hyperplasie Congénitale des Surrénales (HCS) : Où en sommes nous en 2013 ?

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Les organes génitaux de la fille porteuse d'une HCS diffèrent de l'anatomie habituelle par : 1) L'absence d'ouverture vaginale visible, la cavité vaginale s'ouvrant dans la paroi de l'urèthre ; 2) Un développement excessif du clitoris (tubercule génital) ; 3) Une fusion variable des grandes lèvres . Ces caractères sexuels sont variables d'une enfant atteinte à l'autre, en fonction du type de mutation génique impliqué dans l'HCS) et du traitement reçu par l'enfant.

La reconstruction des organes génitaux de la fille porteuse d'une HCS comporte trois étapes essentielles : 1) L'ouverture de la cavité vaginale au périnée et sa séparation de la voie urinaire ; 2) La réduction éventuelle du tubercule génital ; 3) La reconstruction de l'anatomie habituelle de la vulve.

Un certain nombre de questions et de dilemmes sont d'actualité dans la prise en charge chirurgicale des HCS : 1) Le timing de cette chirurgie : Certains (dont nous sommes) préfèrent réaliser une reconstruction précoce car la qualité des tissus génitaux est favorable à la reconstruction génitale et car les parents souhaitent redonner à leur petite fille une anatomie la plus proche possible de la normalité en limitant l'impact psychologique de l'hospitalisation ; d'autres préfèrent attendre que l'enfant soit en âge de comprendre pour adhérer au traitement et pour éviter une reprise chirurgicale possible à l'adolescence lorsque la chirurgie a été réalisée précocement. La chirurgie tardive a sans doute un retentissement psychologique plus lourd, surtout si elle est réalisée dans la période difficile de l'adolescence. Elle n'est pas dénuée de problèmes car cette chirurgie peut être plus lourde et non dénuée non plus de complications. Peu de chirurgiens connaissent cette chirurgie chez l'adolescent. 2) La réduction de la taille du clitoris peut affecter la sensibilité de cet organe et les quelques rares études cherchant à évaluer la qualité de la vie sexuelle des patientes opérées montrent, pour plusieurs, une qualité de vie sexuelle peu satisfaisante. D'autres études sont beaucoup plus encourageantes.3) Nous évaluons de nos jours les résultats de chirurgies pratiquées il y a plus de 20 ans suivant des techniques qui ont considérablement évolué depuis. Les résultats des techniques actuelles qui préservent beaucoup mieux les nerfs donnant la sensibilité au clitoris et reconstruisant plus correctement l'entrée du vagin (introitus), ne seront connus que dans plus de 15 ans. Là réside toute la difficulté de l'appréciation des traitements proposés. 4) Le traitement prénatal précoce par la Dexaméthasone dans les familles où existe déjà un enfant atteint, a été et reste un espoir pour éviter les anomalies génitales de l'HCS. Il y a cependant un certain nombre de réserves qui sont émises sur les effets secondaires possible de ces traitements sur l'enfant et la mère.

Il naît en France chaque année 50 enfants porteurs d'une HCS dont 25 filles, or il y a près de 30 centres hospitaliers et universitaires. Il est clair que la complexité de ces prises en charge de l'HCS et l'environnement multidisciplinaire qu'elles imposent, demandent que soient clairement identifiés sur notre territoire des centres de références. De même, les programmes internationaux de recherche et de collaboration doivent se poursuivre pour continuer d'améliorer les traitements proposés, à l'écoute des patientes.

Notes

Surgical management of genital organs in girls with congenital adrenal hyperplasia: a population-based national study

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Background

Despite the major long-term influence of feminizing surgery in girls with CAH, little is known of its use at a population level.

Patients and methods

We analyzed the initial surgical procedure performed in a population-based cohort of all 167 girls with CAH born in France from 1996 to 2003. Patients charts and operating reports were evaluated regarding patient characteristics, urethro-vaginal confluence, surgery (age, surgical technique, type of clitoral surgery and of vaginal reconstruction) and the hospital center where the surgery was performed. 5 aspects of the initial management were scored as appropriate or inappropriate regarding current international recommendations.

Results :

167 patients were identified and 142 (85%) were operated at a median age of 170 days. Of those 142, 14 (10%) were classified as Prader I or II and 128 (90%) were classified as Prader III to V. In Prader III to V cases, urethro-vaginal confluence was low in 96/127 (76%) and high in in 31/127 (24%). Vaginal reconstruction consisted in Fortunoff flap (n = 71), partial urogenital mobilization (n = 17), total urogenital mobilization (n = 5), vaginal pull-through (n = 31) or others (n = 9). Clitoral surgery was performed in 88% of patients and consisted mostly in corporal tissue excision with preservation of glans and his neurovascular bundles.

The 142 patients were operated at 31 institutions throughout the country: 46% of patients were operated in high-caseload institutions (more than 8 patients during the 8-year period), 37% in medium-caseload institutions (4 to 7 patients) and 17% in low-caseload institutions (3 patients or less). Using a 5 points scoring system, 48/138 patients (35%) had an adequate management on all items while 40 (29%) had a near-optimal management (score of 4/5). Optimal management was associated with high hospital caseload (OR 7.3, 95% CI 2.1-25.7).

Conclusion :

Our results show a wide heterogeneity of surgical techniques performed in a large and heterogeneous number of institutions throughout the country. Adequacy of management was strongly associated with the patient caseload suggesting the need for performing this rare surgery in a limited number of institutions throughout the country.

Notes

Predictive factors of health status of patients with congenital adrenal hyperplasia due to 21-hydroxylase diagnosed during childhood

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Adult patients with congenital adrenal hyperplasia (CAH) often suffer from long-term complications as obesity, osteoporosis and perturbation of the reproductive axis leading to infertility. Nevertheless, these complications did not concern all CAH patients, and predictive or causal factors responsible for such complications are not well established yet. We therefore proposed to studied adult CAH patients status in term of body mass index (BMI), bone mineral density (BMD), adrenal CT-scan and reproductive parameters and to determined factors that could account for such complications. Hundred and four patients (71 women, 33 men, 52 with salt-wasting form, 17 with virilizing form and 35 with non classical form of CAH) were studied. Mean age was 27.9 years (16-52). Among the 71 women, 52% have a BMI>25 kg/m², 50% irregular menstrual cycles, 35% hirsutism, 48% abnormal BMD (osteopenia or osteoporosis) and 54% adrenal hyperplasia on CT-scan. Among the 33 men, 40% have a BMI>25 kg/m², 36% adrenal rest tumors, 78% abnormal BMD and 57% adrenal hyperplasia on CT-scan. In univariate analysis, predictive factors for BMI>25 kg/m², abnormal CT-scan, presence of hirsutism or irregular menstrual cycles in women were all related to hormonal control of CAH, including 17OHprogesterone, androstenedione or ACTH levels ($p<0.05$). Predictive factors of abnormal BMD were weight and LH levels ($p<0.05$). Predictive factor of the presence of adrenal rest tumors was the severity of the disease, i.e. the presence of classical form of CAH ($p=0.002$). Total cumulative (TCG) glucocorticoid doses were calculated from pediatric and adult files in 71 patients and were significantly associated to BMI ($p=0.01$) and abnormal CT-scan ($p=0.05$).

This study confirms the high prevalence of long-term complications in adult CAh patients and highlights the predominant role of hormonal control in the development of these complications. Such data are of importance in improving the management of patients with CAH and in acquiring further knowledge for use in the design of novel therapeutic interventions that aim to improve patient outcome. Finally, it highlights the importance of long term follow up of these patients and of transitional care between childhoods to adult life.

Notes

New therapeutic approaches in CAH

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Cortisol is an essential stress hormone and replacement with oral hydrocortisone is lifesaving in patients with adrenal insufficiency. Cortisol has a diurnal rhythm regulated by the central circadian oscillator (body clock) located in the suprachiasmatic nucleus of the hypothalamus. Cortisol levels start to rise between 3 and 4am, peak within an hour of waking, fall over the day with a quiescent period starting around 7pm and nadir levels occur at midnight1. This rhythm is an important metabolic signal for peripheral tissue clocks and loss of cortisol rhythmicity is associated with fatigue, depression and insulin resistance2. A general principle in endocrinology is to replace hormones to replicate physiological levels. However, the pharmacokinetics of oral immediate release hydrocortisone make it impossible to replicate the overnight rise in cortisol and patients with adrenal insufficiency wake with low cortisol levels at the time when their cortisol level should be peaking. Patients with congenital adrenal hyperplasia have the additional problem that the increased early morning ACTH drive from the pituitary, in the absence of cortisol feedback, results in a rise in adrenal androgens. Patients with adrenal insufficiency, both primary and secondary, still have an increased morbidity and mortality despite current replacement regimens, and a major complaint is fatigue5. Patients with CAH, despite a large number of different glucocorticoid treatment regimens, also have poor health outcomes. A recent large cohort study in the UK, CaHASE, has revealed evidence of greatly impaired health status in adult patients with CAH6. Thus, there is a need for physiological circadian cortisol replacement to address some of these issues. Preliminary evidence, using intravenous infusions of hydrocortisone, suggest that provision of circadian cortisol levels with an overnight rise can improve both biochemical control of CAH7. The challenge is to generate an oral modified release formulation of hydrocortisone that can replicate the overnight rise in cortisol and formally test health benefits. Chronocort is a new approach to delivering hydrocortisone therapy1. This modified release formulation replaces the overnight circadian rhythm of cortisol. Pilot formulations have demonstrated the ability to mimic the circadian cortisol rhythm in normal volunteers and studies in patients with CAH have confirmed the ability to control morning androgen levels. In conclusion, there is a need to develop new formulations of glucocorticoid replacement and Chronocort provides one option for addressing this challenge.

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Notes

The role of Therapeutic Education in the treatment of Congenital Adrenal Hyperplasia (CAH)

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Therapeutic education is a practice that cannot be separated from care, which since the 70s has undergone continual growth in hospital departments and then in doctor's offices.

This growth relies on numerous works used to characterize this practice and assess the impact on patients and on the organization of the health system.

These works led to its recognition by the WHO in 1998, by HAS in 2007 and more recently by the 2009 law on Public health. The therapeutic education is to teach patients self-care skills and encourage them to adapt to the illness which when applied to their daily life enables them to better manage their illness and provide a better quality of life. This transformation in the role of the patient - for some similar to a silent revolution (5) - places the patient as the special learner because it is now question of acquiring skills recognized as essential to maintain and improve health, avoid incidents and delay complications. (4)

To be looked after now requires learning how to look after oneself.

This therapeutic education relies on principles and educational patterns and is achieved through educational activities or real structured programs in hospitals. (2) (3)

In our endocrinology department - reproductive medicine, an ETP program was developed for patients diagnosed with HCS. This is a chronic pathology requiring life-long treatment and often for women carrying the disease virilisation of genitals.

The innovative character of this program lies in planning collective sessions (over one day) in alternation with the individual medical consultations already integrating an educational dimension. This is manifested by explanations from carers having already determined the knowledge level of the patient and having understood their questions. The collective sessions come complement these first skill learning sessions by allowing the patients to reflect on their concept of the disease and the treatment, to identify risk situations, to adapt the treatment, to express their feelings about their disease and, last but not least, to confirm emergency procedures such as hydrocortisone injections.

An additional collective session is organized for the women; this session concerns the patient's reflection on the implications of HCS on their personal, emotional and sexual life. Exchanges between peers encourage and support their self-respect and self-confidence in these areas.

To date, five women followed the entire program; an evaluation will be offered. But they were already able to express, in addition to their total satisfaction, the changes that took place during the months following the first ETP day. These changes concern their physical self-image and their ability to enter into relationships, and for two of them to accept a love relationship. They told of having taken advan-

tage of the experience of the other patients and feeling reassured on their feeling with respect to the difference with others.

Six men participated in the first day of the program and announced their satisfaction in meeting other patients with the same disease, being able to express their fatigue, and confirming their knowledge of the treatment.

Notes

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www.surrenales.com

Journée Association Surrénales

Hyperplasies Congénitales des Surrénales

Avec le parrainage de la SFE et de la SFEDP

Amphithéâtre Pierre Laroque
Ministère des Affaires sociales et de la Santé

SFE

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Centre de Référence des Maladies Endocriniennes Rares de la Croissance

SFEDP Société Française d'Endocrinologie et Diabétologie Pédiatrique

avec le soutien institutionnel du Laboratoire HRA Pharma

HRA Pharma
ENDOCRINOLOGY