Article:
Merke, D.P., Mallappa, A., Arlt, W. et al. (14 more authors) (2020) OR25-02 A phase 3 study of a modified-release hydrocortisone in the treatment of congenital adrenal hyperplasia. Journal of the Endocrine Society, 4 (Supplement_1).

https://doi.org/10.1210/jendso/bvaa046.214

the inhibitory role of estrogen in the male HPG axis. Clinicians may consider this rare diagnosis for men in their late teens or early twenties, who have spontaneous initiation of puberty, presenting with bone pain and continued linear growth.

Adrenal

ADRENAL - HYPERTENSION

Clinical Factors Associated with Insulin Secretion and Sensitivity in Patients with Primary Aldosteronism

Yuya Tsurutani, MD, PhD, Sho Katsuragawa, MD, Tomoko Takiguchi, MD. PhD, Jun Saito, MD. PhD, Masao Omura, MD, PhD, Tetsuo Nishikawa, MD,PHD.
Yokohama Rosai Hospital, Yokohama, Japan.

MON-215

Introduction: Primary aldosteronism (PA) is associated with an increased risk of impaired glucose tolerance or type 2 diabetes mellitus. Previous studies have reported that impaired insulin secretion and insulin sensitivity in PA may lead to impaired glucose tolerance. However, the relationship between PA and glucose tolerance, and the factor associated with these glucose metabolism abnormalities is not well understood. In particular, few studies have analyzed the association between aldosterone excess and insulin sensitivity or resistance after the adjustment for other clinical variables. In this study, we analyzed the associations between multiple clinical variables observed in PA and the indices of insulin sensitivity and resistance, using the result of 75 g oral glucose tolerance test (OGTT).Method: This was a retrospective observational study that analyzed the data of 646 patients with PA who underwent adrenal venous sampling and 75 g OGTT. The insulinogenic index and Matsuda index, indices of insulin secretion and sensitivity, respectively, were calculated from the results of a 75 g OGTT. Correlations between these indices and the multiple clinical variables were analyzed. In addition, we performed multiple regression analyses to identify the independent explanatory variables of these indices.Results: Insulinogenic index had positive correlations with the body mass index (BMI), alanine aminotransferase (ALT) level, triglyceride (TGL) level, and potassium level, and negative correlations with both age and plasma aldosterone concentration (PAC). In a multiple regression analysis, both the age (β = -0.231, $p < 0.001$) and potassium level (β = 0.175, $p = 0.002$) were selected as the independent explanatory factors. The Matsuda index had positive correlations with the PAC and cortisol level after a 1 mg dexamethasone suppression test (DST), and negative correlations with BMI, ALT level, TGL level, plasma renin activity (PRA), and potassium level. In a multiple regression analysis, BMI (β = -0.216, $p < 0.001$), ALT level (β = -0.290, $p < 0.001$), TGL level (β = -0.225, $p < 0.001$), the cortisol level after 1 mg DST (β = 0.124, $p = 0.009$), and PRA (β = -0.119, $p = 0.019$) were selected as the independent explanatory factors. Conclusion: In PA patients, older age and decreased potassium levels were associated with impaired insulin secretion. An increase in the variables associated with metabolic abnormalities such as BMI, ALT, and TGL were associated with decreased insulin sensitivity. In addition, we found that decreased PRA was associated with increased insulin sensitivity.

Adrenal

ADRENAL MEDICINE — CLINICAL APPLICATIONS AND NEW THERAPIES

A Phase 3 Study of a Modified-Release Hydrocortisone in the Treatment of Congenital Adrenal Hyperplasia

Deborah P. Merke, MS, MD[1], Ashwini Mallappa, MD, MHSc[2], Wiebke Arlt, MD DSc FRCP FMedSci[3], Aude Brac de la Perriere, MD[4], Angelica Linden Hirschberg, MD, PhD[5], Anders Juul, MD,PHD,DMSC[6], John D. C. Newell-Price, MD, PhD, FRCP[7], Colin Graham Perry, MRCP,PHD, MD[8], Alessandro Prete, MD[9], Aled Rees, MD,PHD[10], Nicole Reisch, MD[11], Monica Stikkelbroeck, MD,PHD[12], Philippe A. Touraine, MD,PHD[13], Kerry Maltby, BSc[14], Peter Treasure, PhD[15], John Porter, MD[14], Richard John M Ross, MBBS,FRCP,MD[7].
[1]NIH, Bethesda, MD, USA, [2]NIH, Rockville, MD, USA, [3]Univ of Birmingham, Birmingham, United Kingdom, [4]Hôpital Louis Pradel, Bron, France, [5]Karolinska Institutet, Stockholm, Sweden, [6]Rigshospitalet, Copenhagen, Denmark, [7]University of Sheffield, Sheffield, United Kingdom, [8]Queen Elizabeth University Hospital, Glasgow, United Kingdom, [9]University of Birmingham, Birmingham, United Kingdom, [10]Cardiff University, Cardiff, United Kingdom, [11]Medizinische Klinik und Poliklinik IV, Klinikum der Universität München, Munich, Germany, [12]Radboud Univ Nijmegen Med Ctr, Nijmegen, Netherlands, [13]GH Pitie Salpetriere, Paris Cedex 13, France, [14]Diurnal Ltd, Cardiff, United Kingdom, [15]Statistical Services Ltd, Kings Lynn, United Kingdom.

OR25-02

Background: Patients with congenital adrenal hyperplasia (CAH) due to classic 21-hydroxylase deficiency have poor health outcomes related to inadequate glucocorticoid (GC) replacement. We compared disease control of adults with classic CAH treated with a modified release hydrocortisone (MRHC), which replicates physiological diurnal cortisol secretion, versus standard GC therapy.

Methods: 6 month, open label, study in 122 patients randomised either to treatment with MRHC (Chronocort®, Diurnal Ltd, Cardiff, UK) twice daily at ~ 0700h & ~2300h, or to remain on their standard GC regimen (hydrocortisone, prednisolone, prednisone, dexamethasone). Patients had 24-hr profiling of serum 17-hydroxyprogesterone (17-OHP) at baseline and for dose titration at 4 and 12 weeks. The primary efficacy endpoint was the change from baseline to 24 weeks in the natural logarithm of the mean of the 24-hr standard deviation score (SDS) profile for 17-OHP.

Results: Both groups achieved improved hormonal control at 24 weeks. The mean 24-hour 17-OHP SDS was significantly lower on MRHC compared to standard GC at 4 weeks ($p = 0.0074$) and 12 weeks ($p = 0.019$), but not at 24 weeks. In post-hoc analyses at 24 weeks, MRHC treatment showed a greater reduction in 17-OHP SDS compared to standard GC in the morning, 0700-1500h ($p = 0.0442$) and a greater reduction in log transformed 17-OHP 24 hour AUC ($p=0.0251$). Defining a morning 17-OHP <1200ng/dl (<36 nmol/L) as good control, for patients not controlled at baseline 85% were well controlled at 24 weeks with

MHRC versus 50% on standard GC. For patients controlled at baseline 100% were controlled at 24 weeks on MHRC versus 84% with standard GC (p = 0.0018). The variability of 17-OHP over 24 hours was significantly reduced in the MRHC group compared to standard GC: the ratio of amplitude at 24 weeks divided by amplitude at baseline was for MRHC, 0.361 [95% CI: 0.235, 0.651], and standard GC, 0.917 [0.773, 1.366]; (p = 0.0001).There were no adrenal crises on MRHC and fewer stress doses despite similar incidence of inter-current illness to the standard GC group which had 3 adrenal crises. MRHC was associated with patient reported benefit including restoration of menstruation in 4 patients on MRHC and 1 on standard GC and two partner pregnancies in patients on MRHC and none on standard GC.

Discussion: This is the largest randomised controlled trial of GC treatment in CAH and showed that intensification of therapy could improve control of the androgen-precursor, 17-OHP, and that this hormonal control was superior in the morning with MRHC. MRHC reduced the fluctuations in 17-OHP such that in the majority of patients the 17-OHP profile was within the reference range throughout 24 hours, providing consistent and optimal disease control.

Conclusion: Diurnal cortisol replacement with a MRHC improves the biochemical control of classic CAH with a twice-daily therapeutic regimen.

Pediatric Endocrinology

PEDIATRIC PUBERTY, TRANSGENDER HEALTH, AND GENERAL ENDOCRINE

Somatic and Neurodevelopmental Outcome and Muscle Tone in 5 to 9 Year Old Children Born After Intracytoplasmic Sperm Injection

Marta Snajderova, MD,PHD[1], Josef Kraus, MD, PhD[2], Daniela Zemkova, Dr, PhD.[1], Tonko Mardesic, MD, PhD[3].
[1]University Hospital, Charles University - [2]nd Medical Faculty, Dept. of Pediatrics, Prague 5, Czech Republic, [2]University Hospital, Charles University - [2]nd Medical Faculty, Child Neurology Dept., Prague 5, Czech Republic, [3]Department of Reproductive Medicine, Sanatorium Pronatal, Prague 4, Czech Republic.

SUN-076

Introduction: Assessing the development and health status of children born after assisted reproductive techniques is very important. This also applies to somatic and neurological development. Little is known on the development of muscle tone in children. Aim of our study was to evaluate the somatic and neurological development in children born after intracytoplasmic sperm injection (ICSI) with special focus on proximal muscle tone.

Material and methods: A group of 82 singletons (ICSI) aged 5–9 years (42 M, 40 F) and a control group of 82 singletons spontaneously conceived (SC), all with low morbidity, were compared by age and sex. Comprehensive assessment by endocrinologist, clinical anthropologist and pediatric neurologist was performed.

Results: Both ICSI and SC children had normal somatic development. In the standard neurological testing, motor development did not differ significantly in ICSI children compared with the general population. Nevertheless, some coordination abnormalities tested by diadochokinesis and by the finger-nose test, were found in all but 7 ICSI children (ICSI in 91 % versus SC in 9 %; p<0.001). A prominent hypotonia of upper girdle muscles tested by the scarf sign was found in all but 4 ICSI children (ICSI in 95 % versus SC in 61 %; p<0.001). In the contrary, no difference was found for lower girdle muscle tone in ICSI versus SC children. Any of the factors tested for possible relationship to upper girdle muscle hypotonia was not found to be significant.

Conclusions: As far as we know, this study is the first evaluation of proximal muscle tone in ICSI children aged 5 - 9 years. Subtle changes in the neurological status were revealed comparing ICSI and SC children, i. e. the prominent upper girdle muscle hypotonia and the coordination changes. The hypotonia can be explained by a slight change in the muscle tone maturation and movement coordination. The ICSI method very likely does not have any negative effect on the neurodevelopmental outcome of children. Nevertheless, the development of muscle tone and coordination in ICSI children should be monitored. Early diagnosis of these abnormalities helps to early initiation of appropriate therapy and thus avoids possible complications.

Pediatric Endocrinology

PEDIATRIC ENDOCRINE CASE REPORTS II

Hyperinsulinemic Hypoglycemia Responsive to Diazoxide Due to a Previously Unknown ABCC8 Dominant Mutation

Veronica M. Figueredo, MD, Alejandro Diaz, MD, Pedro Pagan Banchs, MD.
Nicklaus Children's Hospital, Miami, FL, USA.

MON-073

Background: Hyperinsulinism is the most common cause of persistent hypoglycemia. It results from different genetic defects, the most common being recessive and dominant mutations in the ABCC8/KCNJ11 genes. The majority of recessive mutations have a poor response to Diazoxide, while dominant mutations are highly variable in both clinical presentation and response to treatment. Prompt recognition and management is critical to avoid irreversible brain damage. **Clinical case:** A 38-week gestation male, born via emergent c-section due to decreased fetal movement, presented with neonatal hypoglycemia. Pregnancy was uncomplicated and mother had a normal OGTT. Patient had a history of suspected sepsis, seizures, pulmonary hypertension and respiratory distress requiring intubation. Blood glucose was undetectable at birth and required multiple dextrose 10% boluses. A critical sample with a glucose of 47 mg/dL showed an elevated insulin at 30.3 m IU/mL with undetectable ketone levels. Lactic acid, ammonia, cortisol, GH, plasma amino acids, acylcarnitine profile and uric organic acids where all normal for a hypoglycemic state. He required intravenous glucose infusion with GIR up to 17 mg/kg/min to maintain normoglycemia. A brain MRI at 11 days of life showed findings of white matter injury. Subsequent genetic testing identified a heterozygous c.4051G>A (p.Val1351Met) variant in ABCC8, classified as "of uncertain significance". However, an entry