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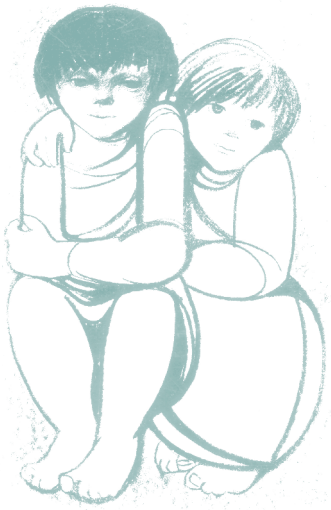
XLVII Conferências de Genética Doutor Jacinto Magalhães

Abstracts Book



XLVII Conferências de Genética
Doutor Jacinto Magalhães

11 DE MAIO 2018

A GENÉTICA NA ENDOCRINOLOGIA E NO METABOLISMO

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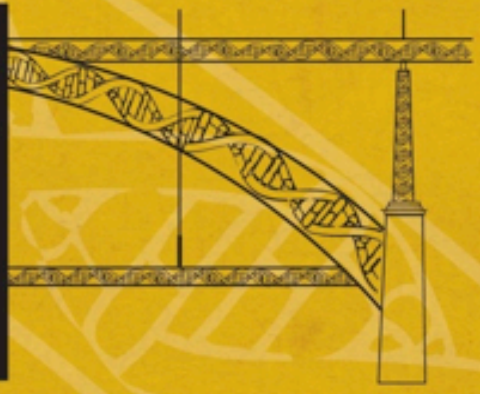

— Baixa Estatura
— Hiperplasia Congénita da Supra Renal
— Diabetes Hereditária
— Metabolismo: Novos Desafios e Novas Terapêuticas

PRÉMIO PARA MELHOR TRABALHO

RESUMOS PUBLICADOS EM REVISTA INDEXADA

Submissão de resumos até 25 de Abril de 2018

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8:30H Secretariado | Registration Opening

9:00H **Sessão de Abertura | Opening & Welcome**
Ana Maria Fortuna (*CHP*), José Barros (*CHP*)

9:15H **BAIXA ESTATURA | SHORT STATURE**
Moderadores: **Teresa Borges** (*CHP*), **Natália Oliva-Teles** (*CHP*)

Abordagem do Endocrinologista Pediátrico | *Pediatric Endocrinologist Approach*
Cíntia Castro-Correia (*CHSJ*)

Pistas para o Diagnóstico: Avaliação do Raio-X | *Clues to Diagnosis: X-Ray Evaluation*
Filipe Macedo (*ICUF Porto e Unilabs*)

Abordagem do Geneticista Clínico | *Clinical Geneticist Approach*
Ana Rita Soares (*CHP*)

10:30H Pausa para café | ***Visita a Posters***
Coffee Break | ***Posters Viewing***

11:00H **HIPERPLASIA CONGÉNITA DA SUPRA-RENAL | CONGENITAL ADRENAL HYPERPLASIA**
Moderadores: **Catarina Limbert**, (*CHLC/HDE*), **Rosário Santos** (*CHP*)

Formas Clássicas de Hiperplasia Congénita da Supra-Renal |
Classic Congenital Adrenal Hyperplasia
Maria João Oliveira (*CHP*)

Formas Não Clássicas Hiperplasia Congénita da Supra-Renal |
Non-Classic Congenital Adrenal Hyperplasia
Joana Freitas (*CHP*)

Hiperplasia Congénita da Supra-Renal Devido ao Défice de 21-Hidroxilase: Aconselhamento Genético |
Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency: Genetic Counseling
Natália Tkachenko (*CHP*)

Hiperplasia Congénita da Supra-Renal e Gravidez |
Congenital Adrenal Hyperplasia and Pregnancy
Joana Vilaverde (*CHP*)

12:15H **COMUNICAÇÕES ORAIS SELECIONADAS | SELECTED ORAL COMMUNICATIONS**
Moderadores: **Mariana Monteiro** (*ICBAS*), **Paula Jorge** (*CHP*)

13:15H Almoço | ***Visita a Posters***
Lunch | ***Posters Viewing***

14:30H **DIABETES HEREDITÁRIA | HEREDITARY DIABETES**
Moderadores: **Helena Cardoso** (*CHP*), **Lúcia Lacerda** (*CHP*)

Hipoglicemias Hiperinsulinémicas e Diabetes Mellitus |
Hyperinsulinemic Hypoglycemia and Diabetes Mellitus
Khalid Hussain (*Weill Cornell Medicine*)

Apresentação de Casos Clínicos | Clinical Cases Discussion
Sofia Bota (*CHLC/HDE*), ***Catarina Limbert*** (*CHLC/HDE*),
Catarina Figueiredo (*CHP*), ***Teresa Borges*** (*CHP*)

16:00H Pausa para café | ***Visita a Posters***
Coffee Break | ***Posters Viewing***

16:30H **METABOLISMO: GRAVIDEZ E NOVAS TERAPÊUTICAS |**
METABOLISM: PREGNANCY AND NEW THERAPIES
Moderadores: Esmeralda Martins (*CHP*), Manuela Ferreira de Almeida (*CHP*)

Novos Desafios no Seguimento da Gravidez nas Doenças Hereditárias do Metabolismo |
The New Challenges in the Management of Pregnancy in Inherited Metabolic Disorders
Ana Cunha (*CHP*)

Novas terapêuticas | *New Therapies*
Anabela Bandeira (*CHP*)

17:30H **Entrega de Prémios e Sessão de Encerramento | Awards Ceremony and Closing Session**
Ana Maria Fortuna (*CHP*), Mariana Monteiro (*ICBAS*) e Elisabete Almeida (*APOFEN*)

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PALETRAS | LECTURES

BAIXA ESTATURA | SHORT STATURE

Abordagem do Endocrinologista Pediátrico | *Pediatric Endocrinologist Approach*

Cíntia Castro-Correia
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Departamento de Pediatria, Centro Hospitalar de São João

Growth assessment is one of the challenges most often encountered by the Pediatric Endocrinologist. Being growth dependent on multiple factors, but ultimately involving the elongation of the long bones, it becomes fundamental to understand the physiology of the epiphyseal or growth plates.

Taking into account the definition of short stature, the clinical perspective of the Pediatric Endocrinologist will be analyzed, paying particular attention to the main etiologies of short stature that determine therapeutic attitudes with an impact on the health and quality of life of children and young people.

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PALETRAS | LECTURES

BAIXA ESTATURA | SHORT STATURE

Pistas para o Diagnóstico: Avaliação do Raio-X | *Clues to Diagnosis: X-Ray Evaluation*

Filipe Macedo
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ICUF Porto e Unilabs

A intervenção do Rx convencional no algoritmo de avaliação da baixa estatura faz-se em dois momentos. Inicialmente no estudo da idade óssea através do Rx da mão e punho, importante no estudo de todos os tipos de baixa estatura. Depois, na avaliação de causas patológicas de baixa estatura através do Rx do esqueleto, mais frequentemente associadas a displasias ósseas.

Descrevem-se os fundamentos e aplicações dos principais métodos de determinação da idade óssea por Rx e alguns dos achados radiográficos mais frequentes nas displasias associadas a baixa estatura.

PALETRAS | LECTURES

BAIXA ESTATURA | SHORT STATURE

Abordagem do Geneticista Clínico | *Clinical Geneticist Approach*

Ana Rita Soares
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Unidade de Genética Médica, Centro de Genética Médica Doutor Jacinto Magalhães, Centro Hospitalar do Porto

Short stature is a common problem in Paediatrics and also a feature of many genetic syndromes. It is defined as a length/height <0.4th centile. The two most common causes for short stature, accounting for 75% of cases, are familial short stature and constitutional delay of growth and puberty. In the remaining causes, genetic etiology accounts for about 15% of cases: syndromes, chromosomal anomalies, skeletal dysplasias and GH deficiency and receptor insensitivity.

The Geneticist approach to short stature includes its categorization into one of the five clinical groups: isolated short stature; short stature with history of low birth weight; disproportionate growth; short stature with dysmorphic features and mild or no mental retardation; short stature with moderate mental retardation. After exclusion of familial short stature or constitutional delay, genetic studies are chosen according to clinical characteristics presented by the child as well as his family history.

The best care and approach for short stature patients is a multidisciplinary team, mainly with paediatric endocrinologist, clinical geneticist, radiologist, laboratory, and others. The genetic diagnosis can help with follow-up and will allow an accurate genetic counselling for patient and family.

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PALETRAS | LECTURES

HIPERPLASIA CONGÉNITA DA SUPRA-RENAL | CONGENITAL ADRENAL HYPERPLASIA

Formas Clássicas de Hiperplasia Congénita da Supra-Renal | *Classic Congenital Adrenal Hyperplasia*

Maria João Oliveira
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Serviço de Pediatria, Centro Materno - Infantil do Norte, Centro Hospitalar do Porto

Congenital adrenal hyperplasia (CAH) refers to a group of inherited enzymatic defects, in cortisol biosynthesis. 21-hydroxilase deficiency (21-OHD), is the most common, and will be review in this presentation, particularly the classic forms with neonatal presentation. It accounts for over 90-95% of CAH cases and when milder and nonclassic forms are included, 21-OHD is one of the most common genetic diseases. The 21-OH enzyme is responsible for the conversion of 17-hydroxyprogesterone (17-OHP) into 11-deoxycortisol and progesterone into 11-deoxycorticosterone, the precursors of cortisol and aldosterone respectively. Human 21 hydroxylase is encoded by CYP21A2 gene, on chromosome 6p21.3. Only 30 Kb away resides the non-functional CYP21A1P pseudogene, which encodes a truncated, inactive enzyme. Both share 98% homology, which favours the intergenic recombinations and gene conversions events during meiosis between the two CYP21A genes.

All forms of CAH are inherited in a monogenic, autosomal-recessive pattern, requiring two mutant 21-OHD alleles to express the disease. About 75% of the patients are compound heterozygotes for two or more different mutant CYP21A2 alleles. The severity of the disease is determined by the activity of the allele less affected. According to the severity of the enzymatic dysfunction there are two clinical forms of presentation: classic and nonclassic. The classic forms are further grouped into salt wasting (SW) and simple virilizing (SV) subtypes, depending on whether or not mineralocorticoid synthesis is sufficiently impaired to regulate the sodium balance. The SW subtype is the more serious form of this disease, affects 75% of patients with classic forms and usually presents between 1st and 3rd week of life. Beside the virilization signs and hypocortisolism, the patients present with mineralocorticoid insufficiency and are prone to volume depletion, dehydration with hyponatremia and hyperkalemia and hypovolemic shock potentially fatal. The SV form presents with prenatal virilization and ambiguous genitalia in girls and hypocortisolism and precocious pseudo-puberty in both sexes. Classic 21-OHD occurs in 1: 10,000 to 1: 20,000 live births worldwide. The diagnosis rests on clinical and hormonal data. As a result of 21-OH dysfunction, upstream steroid precursors accumulate and are diverted towards accessible pathways to form potent androgens. Elevations of 17-OHP, the main substrate of CYP21A2, are the hallmark of 21-OHD, and 17-OHP has been used for both diagnosis and monitoring of the disease. Baseline 17-OHP levels in classic forms are consistently above 10,000 ng/dl. Genetic testing for CYP21A2 detects 90 to 95% of mutant alleles and is useful when steroids results are equivocal or unreliable and for genetic counseling. While the most severe and the mildest forms of the disease tend to maintain some genotype-phenotype correlation, the intermediate forms are often poorly linked with specific gene defects, suggesting other contributors (genetic and environmental) to the phenotypical expression. Glucocorticoids and mineralocorticoids are the mainstays of treatment for 21-OHD. Glucocorticoids exert two principal actions: replacement of the deficient cortisol and suppression of the adrenal androgen overproduction. Hydrocortisone is preferred in children and adolescents, until growth is completed, due to its short action, which limits the potential to suppress growth. A total dose of 10-20mg/m2 daily divided in 3 doses is recommended. Stress doses of glucocorticoids should be given in patients with classic 21-OHD during surgery and physical illness.

The goal of the treatment is avoid hypocortisolism and hyperandrogenism and to allow normal growth and development in order to achieve normal target height. Fludrocortisone acetate 0,05-0,2 mg daily divided in 1-2 doses is necessary in patients with classic 21-OHD. Infants with SW forms need higher doses and additionally require supplementation with sodium chloride (1-2g daily) while the renal function matures. Balancing and accurately monitoring treatment remains clinically challenging.

PALETRAS | LECTURES

HIPERPLASIA CONGÉNITA DA SUPRA-RENAL | CONGENITAL ADRENAL HYPERPLASIA

Formas Não Clássicas da Hiperplasia Congénita da Supra-Renal | *Non-Classic Congenital Adrenal Hyperplasia*

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Nonclassic congenital adrenal hyperplasia (NCCAH) due to 21-hydroxylase deficiency is one of the most common autosomal recessive diseases. It results from mutations in the CYP21A2 gene, with reduced but sufficient enzyme activity (20-50%) to maintain glucocorticoid and mineralocorticoid production, at the expense of excessive androgen production. The defective conversion of 17-hydroxyprogesterone to 11-deoxycortisol results in decreased cortisol synthesis and therefore increased corticotrophin (ACTH) secretion. The resulting adrenal stimulation leads to increased production of androgens.

Children may present with precocious pubarche, accelerated growth or medication-resistant acne. In adolescent girls, NCCAH is characterized by acne, hirsutism and menstrual irregularity, often undistinguishable from the polycystic ovary syndrome. Basal 17-hydroxyprogesterone level of >2ng/ml should suggest the diagnosis and an ACTH stimulation test is the gold standard.

Genotyping and genetic counseling is advisable, as one-half to two-thirds of patients are compound heterozygotes for a severe mutation and have a 2,5% estimated risk of having a child with classic CAH.

Treatment of children with signs of hyperandrogenism and accelerated bone age with glucocorticoids will prevent adult short stature. Treatment of adolescent girls with menstrual irregularities or hirsutism is usually done with oral contraceptives, to avoid prolonged glucocorticoid use.

PALETRAS | LECTURES

HIPERPLASIA CONGÉNITA DA SUPRA-RENAL | CONGENITAL ADRENAL HYPERPLASIA

Hiperplasia Congénita da Supra-Renal Devido ao Défice de 21-Hidroxilase: Aconselhamento Genético | *Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency: Genetic Counseling*

Natália Tkachenko
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Genetic counseling is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, carriers, or at risk of being carriers.

Congenital adrenal hyperplasia due to 21-hydroxylase deficiency (21-OHD CAH) is inherited in an autosomal recessive manner. Most parents of probands are heterozygous for a pathogenic variant. Approximately 1% of pathogenic variants are de novo; thus, 1% of probands have only one parent who is heterozygous. In some instances during evaluation of a proband, a parent not previously known to be affected may be found to have biallelic pathogenic variants and the non-classic form of 21-OHD CAH. At conception, if the parents of a proband are both known to be heterozygotes, each sib has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. An affected individual transmits one pathogenic variant to each child. Given the high carrier rate for 21-OHD CAH, it is appropriate to offer molecular genetic testing of CYP21A2 to the reproductive partner of a proband.

Carrier testing for at-risk relatives and prenatal testing for pregnancies at increased risk are possible if the pathogenic variants in the family are known. About 100 pathogenic variants, including single-nucleotide variants, small deletions, small insertions, and complex rearrangements of the gene, have been described to date. Common CYP21A2 pathogenic variants can be grouped as severe or mild based on residual enzyme activity. Salt-wasting 21-OHD CAH usually has the most severe pathogenic variants (e.g., homozygous deletions) and non-classic 21-OHD CAH usually has one mild variant or both mild variants. Compound heterozygosity is one of the factors underlying phenotypic variation. The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.

PALETRAS | LECTURES

HIPERPLASIA CONGÉNITA DA SUPRA-RENAL | CONGENITAL ADRENAL HYPERPLASIA

Hiperplasia Congénita da Supra-Renal e Gravidez | *Congenital Adrenal Hyperplasia and Pregnancy*

Joana Vilaverde
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Congenital adrenal hyperplasia (CAH) is a group of autossomal recessive disorders characterized by impaired cortisol synthesis in the adrenal cortex. The incidence ranges from 1:10000 to 1:20000 births and is more prevalent in some ethnic groups.

The most frequent form of CAH is caused by mutations in the gene encoding the adrenal steroid 21-hydroxilase enzyme (P450c21). The deficiency of 21-hydroxilase is characterized by cortisol and in some cases aldosterone deficiency associated with androgen excess. The severity of the disease is dependent of the activity of the enzyme.

There are 3 expressions of 21-hydroxilase deficiency clinically identify: classic salt wasting with aldosterone deficiency and androgens excess, classic simple virilizing with manifestations of excess androgens secretion and nonclassic with a less severe hyperandrogenic expression. Abnormal fetal genitalia development, disturbances in sodium homeostasis and blood pressure regulation, postnatal somatic growth disturbance, hirsutism and infertility are some of the clinical presentations. There are found more than 100 mutations on the gene CYP21A2. Salt wasting CAH usually has the most severe pathogenic variants while the nonclassic CAH had one mild allele or both mild alleles.

A person affected with the classic or the nonclassic form may have a child with the classic form. The prenatal diagnosis and treatment are essential. The goal of the therapy is to correct the deficiency in cortisol secretion and suppress androgen overproduction. Glucocorticoid replacement has been the base of the treatment, but new treatment strategies continue to be studied.

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PALETRAS | LECTURES

DIABETES HEREDITÁRIA | HEREDITARY DIABETES

Hipoglicemias Hiperinsulinémicas e Diabetes Mellitus | *Hyperinsulinemic Hypoglycemia and Diabetes Mellitus*

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Hyperinsulinemic hypoglycemia (HH) is a heterogeneous condition with dysregulated insulin secretion which persists in the presence of low blood glucose levels. It is the most common cause of severe and persistent hypoglycemia in neonates and children. Recent advances in genetics have linked congenital HH to mutations in 14 different genes that play a key role in regulating insulin secretion (ABCC8, KCNJ11, GLUD1, GCK, HADH, SLC16A1, UCP2, HNF4A, HNF1A, HK1, PGM1, PPM2, CACNA1D, FOXA2).

The commonest cause of medically unresponsive HH is due to recessive mutations in the genes ABCC8/KCNJ11. Autosomal dominant mutations in ABCC8/KCNJ11 lead to either severe or mild forms of HH and in some cases diabetes mellitus has been reported in some mutations carriers later in life. Histologically, congenital HH can be divided into 3 types: diffuse, focal and atypical. Due to the biochemical basis of this condition, it is essential to diagnose and treat HH promptly in order to avoid the irreversible hypoglycemic brain damage. Recent advances in the field of HH include new rapid molecular genetic testing, novel imaging methods (18F-DOPA PET/CT), novel medical therapy (long-acting octreotide formulations, mTOR inhibitors, GLP-1 receptor antagonists) and surgical approach (laparoscopic surgery).

PALETRAS | LECTURES

DIABETES HEREDITÁRIA | HEREDITARY DIABETES

Apresentação de Casos Clínicos | *Clinical Cases Discussion*

Long-term Challenging Investigation and Treatment in Congenital Hyperinsulinism: Three Case Reports

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Congenital hyperinsulinism (CH) is the most frequent cause of persistent and severe hypoglycaemia in the newborn. Clinical presentation and response to therapy may vary depending on the underlying pathology. To avoid pancreatic surgery, optimizing medical treatment may be defying.

Here we present three cases of CH, first suspected when severe hypoglycaemia presented with high serum insulin levels, two immediately after birth and one at 8 months of age. Inborn glycosylation defects were excluded. Polymerase chain reaction to detect mutations in ABCC8 and KCNJ11 genes was performed in all, but in only one patient two novel heterozygous mutations on KCNJ11 gene were identified (c. 403G>T, p. [Gly135Trp]; c.776A>G, p.[His259Arg]). Next generation sequencing was performed in the other cases. Insufficient response to diazoxide was observed in two (including the patient with KCNJ11 mutations), and therefore octeotride, later replaced by lanreotide, was initiated. On day 10 of diazoxide, one patient developed severe asymptomatic thrombocytopenia and had to switch to lanreotide. Still, recurrent hypoglycaemia is observed. No functional imaging (DOPA PET/CT) was performed. Nowadays, the younger patient presents a mild hypotonia and only one has dysmorphic features.

These cases illustrate the challenges associated with CH management, to avoid extensive surgery with predictable morbidity. Regarding this option, DOPA-PET scan can be useful to define a diffuse or local lesion, thus improving accuracy of prognosis and finally surgical cure. Successful cases treated with sirolimus have been reported, preventing surgery.

PALETRAS | LECTURES

METABOLISMO: GRAVIDEZ E NOVAS TERAPÊUTICAS | METABOLISM: PREGNANCY AND NEW THERAPIES

Novos Desafios no Seguimento da Gravidez nas Doenças Hereditárias do Metabolismo | *The New Challenges in the Management of Pregnancy in Inherited Metabolic Disorders*

Ana Cunha
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Inherited metabolic diseases comprise a very heterogeneous and numerous group of individually rare diseases. They can present at any age, affect multiple organs and are due to a disruption of a metabolic pathway. They are usually divided in three groups: disorders that give rise to intoxication, involving energy production and involving complex molecules. Most of these diseases have an autosomal recessive or occasionally X-linked inheritance. The prevalence is around 1:2200 live births and this rate appears to be increasing. More enzyme or genetic defects are found as a basis for known syndromes and there is an increased awareness of these diseases.

The neonatal screening program was established in Portugal in 1979 with PKU and includes since 2008, twenty-four metabolic diseases. There are cases that appear during childhood or adolescence and even in adulthood. Sometimes these diseases manifest for the first time during pregnancy, as this state causes extra strain on maternal metabolism, that may result in presenting symptoms of a previously unknown disease or progression of a known one.

A considerable number of IMD are chronic and reduce the quality of life and/or the life expectation of the persons afflicted. They pose a challenge that require interdisciplinary and multiprofessional diagnosis and treatment. The official recognition of 6 national centers of reference in 2016, will help to concentrate existing expertise and serve to ensure proper medical competence.

The early and better treatment of these diseases has led to an increasing number of women reaching the reproductive ages well enough to pursue the wish to have children of their own. Although, in general, outcomes for women and their children are good, these patients present various challenges from the reproductive perspective. Prepregnancy counseling with information on inheritance, options for reproduction, teratogenicity risk, potential impact on maternal health and long-term health of children should be discussed.

There are important adaptations in maternal metabolism during a normal pregnancy to ensure adequate supply of nutrients and energy to the fetus. Women with metabolic disorders often must live with a modified diet and the nutritional requirements of pregnancy need to be carefully planned and monitored. With appropriate management the teratogenic risk of maternal phenylketonuria can be virtually eliminated, and the risk of metabolic decompensation in disorders of energy metabolism or intoxication significantly reduced.

Currently, limited specific guidance, on the management of any single of these conditions in pregnancy, is available, apart from phenylketonuria. Multidisciplinary management, and close liaison between maternal-fetal specialist, metabolic physicians, dietitians with expertise in metabolic diseases, as well as other specialists if there are specific organs affected, is required to care for these women during pregnancy.

PALETRAS | LECTURES

METABOLISMO: GRAVIDEZ E NOVAS TERAPÊUTICAS | METABOLISM: PREGNANCY AND NEW THERAPIES

Novas Terapêuticas | *New Therapies*

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Most inborn errors of metabolism are caused by defective enzymes, which result in insufficient conversion of substrates into products. In many cases, problems arise because of accumulation of toxic upstream substances, the effects of reduced downstream essential compounds, or abnormal alternative substrate metabolism.

Once an IEM is diagnosed, the next challenge is determining the most effective therapeutic options. Treating IEM is a complex undertaking that should be carried out by a multidisciplinary team: a pediatrician, a geneticist, a neuropediatrician, an intensive care specialist, a nutritionist, nurse and physiotherapist.

Therapies for inborn errors of metabolism use several approaches: restriction of substrate build-up by means of diet or enzymatic inhibition, removal of toxic products, stimulation of residual enzyme activity, replacement of the deficient product.

In the case of lysosomal diseases advances in biotechnology have made possible to produce in laboratories the actual enzymes that are deficient in order to administer them to patients. Furthermore, there are new strategies, involving, for example, recovery of residual enzyme activity using chaperones, cell therapy and gene therapy. Treatment of genetic diseases is a field of medicine that has seen significant advances over recent decades.

Comunicações Orais

Oral Communications

COMUNICAÇÕES ORAIS | ORAL COMMUNICATIONS

CO.1 - CYP21A2 Gene Duplication with a Severe Pathogenic Variant is a Benign Allele that does not Confirm Clinical Suspicions of 21-Hydroxylase Deficiency

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Congenital Adrenal Hyperplasia (CAH), one the most common autosomal recessive disorders, is regularly managed during genetic counselling (GC). The coding gene (CYP21A2) for 21-hydroxylase (21-OH), is located (in cis) with its pseudogene (CYP21A1P) in the RCCX cluster (6p21.3) and, the most common structure of this cluster comprises a single copy of each one. However, genotypes associated with CYP21A2 duplications can be detected in individuals during familial and/or pre-conceptional studies. In this duplicated alleles, the severe variant c.955C>T p.(Glu319*) is frequently detected, but is usually present in the proximal CYP21A2 copy. This means, that even in the presence of a severe variant, its allele is not pathogenic. Therefore, the aim of this work is to emphasize the importance of a better strategy of molecular analysis and an accurate interpretation of its results, in order to establish a correct genotyping of family members and partners, and provide a more reliable genetic counselling.

In our lab, molecular analysis concerning 21-OHD is based in the following strategy of analysis: i) CYP21A2 specific expand long PCR and digestion with TaqI allowing the identification of CYP21A2-deletions/-conversions/-quimeras; ii) direct sequencing of DNA fragments obtained by nested PCR of each CYP21A2 exons and flanking proximal regions; iii) CYP21A2 copy number detection by Multiplex Ligation-dependent Probe Amplification (MLPA), confirming TaqI digestion results and revealing new data, including CYP21A2 duplications. When appropriate, an additional specific direct sequencing is used to distinguish between proximal and distal CYP21A2 copies of the duplicated alleles.

Until now, we studied 21 individuals with a CYP21A2 duplicated allele, presenting the following genotypes:

CYP21A2 duplication in homozygosity: c.[*12C>T;955C>T];[*12C>T;955C>T], found in one case;

CYP21A2 duplication in heterozygosity:

c.[*12C>T;955C>T];[955C>T], found in one case

c.[*12C>T;955C>T];[293-13C>G;518T>A], found in one case

c.[*12C>T;955C>T];[=], found in 16 cases

c.[*12C>T;955C>T];[*13G>A],found in one case

c.[=;=];[=], found in one case.

The different genotypes found with the CYP21A2 duplication don't influence the main conclusion: all genotypes established are benign, since at least the distal CYP21A2 copy of the duplicated allele has no severe pathogenic variants. Each genotype characterization was only possible with the combined interpretation of MLPA and specific direct sequencing results of the proximal and distal CYP21A2 copies. Without this approach, the majority of these individuals would most likely be genotyped as heterozygous for the c.955C>T severe variant, in a CYP21A2 allele erroneously associated with null 21-OH enzymatic activity, conducting to misguided genetic counselling.

COMUNICAÇÕES ORAIS | ORAL COMMUNICATIONS

CO.2 - Six Cases of Ciliopathies with Endocrine Involvement

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Ciliopathies are a group of disorders characterized by abnormal formation or function of cilia. Bardet-Biedl and Alström syndromes (BBS/AS) are two disorders that belong to this group which have significant endocrine involvement. Both disorders are clinically characterized by obesity, intellectual disability (ID)/ developmental delay (DD) and visual and renal problems. BBS patients may also have polydactyly and most AS patients have hearing loss. Here, we describe 4 cases of BBS and 2 cases of AS diagnosed in our Department. We aim to highlight the phenotypic variability and overlap of these ciliopathies and to show the importance of their diagnosis.

All 6 patients had visual problems, mostly cone-rod dystrophy or photophobia (5/5), nystagmus (3/5) and myopia (2/5); excessive weight/obesity; hypercholesterolemia and mild dysmorphic features. All but one AS patient had learning difficulties or mild DD/ID; moreover, 3 patients with BBS and one patient with AS had behavioral problems. Two patients with BBS had hypogenitalism, but only one AS patient had hypertrigliceridemia and hyperinsulinemia.

Two BBS patients were siblings. The girl, currently aged 18, also had rhinosinusitis. The boy, aged 14, had macrocephaly, hepatic steatosis, gastro-esophageal reflux and gastritis. The same compound heterozygous variants in the BBS2 gene were found in both.

The other patients with BBS were a 14-year-old boy who also has hearing loss due to serous otitis, postaxial feet polydactyly and bifid right thumb, and a 48-year-old man who also has postaxial polydactyly of the hands and feet and renal cysts. The former has a homozygous variant in the BBS10 gene. The latter has two compound heterozygous variants in the BBS2 gene.

One of the AS patients, a 12-year-old girl, also had precocious puberty and mild to moderate hearing loss. The other patient with AS was a 3-year-old boy who had transient dilated cardiomyopathy. Both have homozygous variants in the ALMS1 gene.

All patients had retinal disease, excessive weight, dyslipidemia and dysmorphisms. Although learning difficulties are a major feature of these syndromes, one of our AS patients had normal intelligence. Similarly, only one AS patient had hyperinsulinemia and not all BBS patients had polydactyly. Thus, BBS and AS should be considered in patients with cone-rod dystrophy and excessive weight, with or without other features. Of note, the diagnosis of these conditions is clinically important because other features may appear in time and preemptive surveillance, including ophthalmological, endocrinological, renal and, in the case of AS, audiological evaluations, is essential. The utility of NGS for the diagnosis of these overlapping ciliopathies is unquestionable due to the broad number of causative genes, in particular for BBS and as shown by our cases.

COMUNICAÇÕES ORAIS | ORAL COMMUNICATIONS

CO.3 - Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency: Genotype-Phenotype Correlation

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Congenital adrenal hyperplasia is a group of autossomal recessive hereditary diseases that compromise cortisol synthesis. About 95% of cases occur due to 21-hydroxylase deficiency by distinct mutations in the CYP21A2 gene. The disease's severity correlates with CYP21A2 allelic variation and there is general, but not precise, correlation between genotype and phenotype.

The aim of this study was to describe the mutational spectrum of CYP21A2 and evaluate genotype-phenotype correlation in a cohort of patients with 21-hydroxylase deficiency.

Retrospective study of 32 unrelated patients with clinical diagnosis of 21-hydroxylase deficiency, followed at the Pediatric Endocrinology department of a level III hospital. Molecular analysis of CYP21A2 was performed and genotype-phenotype correlation was then established.

Genotyping was performed in 32 patients: 8 with classic salt-wasting form (average age of diagnosis 16.4 days; minimum 1 day, maximum 30 days), 7 with classic simple virilising form (average age of diagnosis 3.1 years; minimum 0 days, maximum 7 years) and 17 with nonclassical form (average age of diagnosis 6.3 years; minimum 6 months, maximum 17 years). The most frequent genetic defects in the classic forms were I2 splice (22.5%), I172N (19.3%) and F306+int (12.9%), followed by Q318X (9.7%) and gene deletions (9.7%) and in the nonclassical form, the V281L (69.4%). Two patients (1 classic form and 1 non-classical form) have ongoing genetic study. The overall concordance between genotype and phenotype was 83.3%. Genotype accurately predicted phenotype in 66.7%, 100% and 88.2% of patients with classic salt-wasting, classic simple virilising and nonclassical mutations, respectively.

The frequency of genetic defects in our patients was comparable to similar studies. In most cases there was a good correlation between genotype and phenotype. This study shows that the molecular analysis of CYP21A2 provides useful information in terms of prediction of disease severity, genetic and prenatal counseling.

COMUNICAÇÕES ORAIS | ORAL COMMUNICATIONS

CO.4 - Thyroid Dysfunction - Results of a Multisystemic Evaluation of Mitochondrial Disorders

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Primary mitochondrial diseases may present a multitude of clinical and biochemical features and despite not being the most recognized, endocrine disorders may ensue. Thyroid dysfunction is no exception and recently it has been recognized as a comorbidity in these patients. Since hypothyroidism may exacerbate growth delay commonly observed in children and adolescents with respiratory chain disorders, its early detection is of great importance. Fatigue may also become more evident.

We retrospectively reviewed clinical records and annual assessment of 45 patients with a definite diagnosis of respiratory chain disorder and a minimum 2-year follow-up at our center (excluding those deceased in the first year of life). Thyroid evaluation was based on thyroid-stimulating hormone (TSH) and free thyroxine (T4L) levels. Secondary evaluation included anti-thyroid autoantibodies such as anti-thyroid peroxidase antibodies (anti-TPO), thyrotropin receptor antibodies (TRAb) and thyroglobulin antibodies.

Our sample has a median age of 13 years, 28% older than 18 years-old and 4% deceased in the first years of life (under the age of 5). Average follow-up time was 8 years.

Within our group of patients, 13% had evidence of thyroid dysfunction, with subclinical hypothyroidism being the most common (9%). In secondary evaluation, there was no evidence of auto-immunity. None showed evidence of hyperthyroidism.

Hypothyroidism was present at the time of the diagnosis in 4%. The remaining developed thyroid dysfunction at a median age of 12 years-old, after at least 5 years of follow-up. All patients with thyroid disease have growth delay.

Levotiroxine was started in patients with clinical hypothyroidism (4%): a patient diagnosed in the first months of life achieved normal growth subsequently and a 19-year female improved from fatigue complaints.

Growth delay in children and adolescents with respiratory chain disorders is not only linked with impaired production of energy but instead should be understood as a multifactorial manifestation. Nevertheless, close follow-up is necessary and tiroxine supplementation may be recommended improving growth outcome and quality of life.

COMUNICAÇÕES ORAIS | ORAL COMMUNICATIONS

CO.5 - Characterization of CHP's MODY Patients from Adult's Clinic

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Maturity-onset diabetes of the young (MODY) is a group of monogenic disorders resulting from a primary defect in insulin secretion, associated with pancreatic β-cell dysfunction. MODY can be a suspicion if a type 2 diabetes-like condition occurs in three or more generations and clinical manifestations in young adults, usually before 25 years of age. Approximately 1% of diabetes has a monogenic cause but this is frequently misdiagnosed as type 1 or type 2 diabetes. MODY is a monogenic condition of autosomal dominant transmission, clinically and genetically heterogeneous, with thirteen different genes identified to date. Mutations in the glucokinase (MODY2) and hepatocyte nuclear factor (MODY3 and MODY1) genes are the most common causes of MODY, accounting for about 80% of all MODY patients.

In this review, we summarize the main clinical and molecular characteristics of a group of patients followed at SEndoc and genetically studied at UBG.

This study presents the characterization of 21 patients with clinical diagnosis of MODY type diabetes (belonging to 19 families), out of 102 who underwent molecular genetics testing, Molecular genetics studies were initiated by Sanger sequencing of one or more of the following genes: HNF1A (MODY3), GCK (MODY2), HNF4A (MODY1) and HNF1B (MODY5). As second tier approach, next-generation sequencing (NGS) panel was used.

Sanger sequencing allowed for the identification of the molecular defect affecting 16 families, thus 16% - 61% are MODY3, 33% are MODY2 and 6% are MODY5. NGS panel identified the putative cause of the disease in 3 out of 4 (75%).

Two novel mutations were found: c.863T>C (p.L288P) in GCK and c.2474G>T (p.R825L) in ABCC8.

NGS approach is a valuable tool for such a genetically heterogeneous condition. In this review we outline the importance of an accurate genetic diagnosis in order to help assistant physicians on treatment management reducing the risk of diabetic complications in later life. An early diagnosis is useful for a better outcome but predictive genetic testing for asymptomatic family members may be an issue.

Posters

Posters

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P.01 - Hemoglobinopathies Screening

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The hemoglobinopathies (HGP) are a group of hereditary disorders in which there is abnormal production or abnormal structure of the hemoglobin (Hb) molecule. These are the most frequent group of genetic disorders worldwide. They are broadly categorized into two major groups: thalassemias and structural variants of hemoglobin. HGP have become much more common recently in northern and central Europe, including Portugal, due to immigration.

The aim of this study was to analyze the incidence of HGP in all samples screened for HGP in a central hospital during the last 10 years.

Retrospective study performed in a central and university hospital of Porto, Portugal. A total of 4131 samples of 3886 patients, studied from January 2007 to December 2016, were included. These samples were collected in EDTA-K3 tubes and were analyzed in an automatic hematological counter to obtain red blood cell count with erythrocyte indices. The next step of diagnosis workout consisted on Hb tests: high performance liquid chromatography, electrophoresis and, sometimes solubility test. When detected abnormal structural Hb, samples were tested by molecular biology to identify the Hb variant.

From all the patients studied (n=3886), 19.8% (n=771) had Hb genetic disorders and were subdivided into two main groups: β-thalassemia syndromes (71.5%; n=551) and structural Hb variants (28.5%; n=220). The most frequent HGP were β-thalassemia (n=550 β-thalassemia minor and n=1 β-thalassemia major) and Hb AS (14.5%; n=112), followed by Hb Lepore (5.1%; n=39), Hb SS (2.9%; n=22), Hb AD (2.2%; n=17) and Hb AC (1.0%; n=8). Other rare Hb variants detected were: Hb AE (0.5%; n=4), Hb Indianopolis (0.5%; n=4), Hb Koln (0.4%; n=3), Hb SC (0.4%; n=3), Δ-chain variant Hb A2 (0.3%; n=2), Hb Himeji (0.1%; n=1), Hb Setif (0.1%; n=1), Hb Strasbourg (0.1%; n=1) and Hb Porto Alegre (0.1%; n=1). Concomitant β-thalassemia and Hb AS was also present in two of our patients (0.3%; n=2).

Our data are concordant with previous epidemiological studies. It is noteworthy that our sampling included HGP screening samples and not the whole population and therefore we found higher levels of genetic Hb disorders. The α-thalassemia syndromes were not detected by our methods, as characterization of these diseases requires DNA-based α-globin gene testing. For this reason, some of the samples studied for HGP screening may have gone undetected. HGP are a public health issue and therefore early detection and characterization of the HGP is crucial so that appropriate counselling and treatment can be provided to couples through prenatal screening and families who may be at risk of having HGP. The reinforcement of these measures can lead to the reduction of incidence and morbidity associated with these disorders.

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P.02 - Molecular Diagnosis of CYP21A2 Gene in Affected Cases with Congenital Adrenal Hyperplasia and Familial Implications for Prenatal Diagnosis

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Congenital Adrenal Hyperplasia (CAH) can be due to one of seven different enzymes involved in the synthesis of cortisol. Deficiency in 21-hydroxylase (21-OHD) is responsible for 90 – 95% of the CAH cases. The clinical symptoms of CAH are directly related with 21-OH activity which is associated with the CYP21A2 genotype. CYP21A2 gene cluster is prone to genetic recombination events leading to a wide variety of complex rearrangements (duplications, deletions, conversions) and point mutations. CAH can be divided in two clinical conditions – the classic form [saltwasting (SW) and simple virilising (SV)] and the non-classic (NC) form of the disease. While SW is usually diagnosed in neonates, SV are mainly detected during the first years of life and, most cases of NC-CAH are usually diagnosed from the 4th year of life until puberty or until adulthood.

We present here the molecular results obtained in 265 patients with CAH. The clinical diagnose was established in these patients between the 5th day of life until adulthood (<18 years old). When available, both parents of the affected patients were also analysed after informed consent has been obtained.

Molecular studies of the CYP21A2 gene (using genomic DNA extracted from peripheral blood) included mini-sequencing, expand long PCR, Nested PCR, restriction enzyme digestion, Sanger sequencing, Southern-blotting and/or multiplex ligation-dependent probe amplification (MLPA). Of the 265 patients with CAH, 65 were diagnosed with SW, 51 with SV and 149 with NC-CAH. In 80% of the patients (n=211) the genotype confirmed the diagnosis of CAH due to 21-OH deficiency, in 15% only one pathogenic allele was identified or their genotype was normal for CYP21A2 and in 5% of the cases the pathogenic genotype was not in agreement with the clinical phenotype. In the SW group the most frequent variant was the splicing mutation c.293-13C>G (28.5% of the alleles) which gives rise to a new acceptor splice site in intron 2, in SV patients the missense variant c.518T>A p.(Ile173Asn) was detected in 25.5% of the alleles and, in NC patients the missense variant c.844G>T p.(Val282Leu) was found in 61% of the alleles.

These molecular studies allowed the characterization of the molecular basis of CAH due to 21-OH in this patient's group. Knowing the genotype and the nature/severity of each variant is essential for a correct clinical diagnosis of CAH and for the genetic counselling. With this knowledge, each affected family with CAH can benefit from the cascade genetic screening and, in order to avoid sexual ambiguity in new babies, prenatal diagnosis and treatment during pregnancy, can be offered to couples at risk of having a female child with SW or with the SV-form of CAH due to 21-OH deficiency.

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P.03 - Prematurity and Neonatal Screening

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Worldwide, the birth premature average rate is estimated to be around 10%. Scientific and technological developments in the field of neonatology contributed to the recent significant increase in the survival rate of premature infants and also in Portugal, the number of live premature births has been increasing during the last years, according with data of the Portuguese Society for Neonatology. Nevertheless, the mortality and morbidity of very low birth weight (<1500g) infants is still very high, mainly connected with respiratory failure, infections and congenital malformations. The immaturity and clinical complications associated with prematurity affects newborn screening (NBS) results and may contribute to both false positive and false negative results.

Since 2014, to avoid false negative results for very low birth weight premature infants (birth weight ≤ 1500g or gestational weeks age ≤ 30 weeks), three samples should be taken to these infants for congenital hypothyroidism (CH) newborn screening.

In this study a large cohort of very low birth weight infants, born between 2014 and 2017, was retrospectively analyzed for NBS alterations due to prematurity.

In addition to the know interference in the CH-NBS, alterations could be found in metabolic and cystic fibrosis (CF)-NBS which may be attributed to prematurity. The two additional samples collected for CH-NBS revealed also useful to clarify most altered values found for metabolic and CF-NBS in the first sample, thus avoiding parents' anxiety associated with NBS repetition due to altered values.

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P.04 - Factors Associated with the Performance on the Griffith's Mental Development Scale at Age 6 in Children with Phenylketonuria: Retrospective Cohort Study

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Phenylketonuric (PKU) patients cannot properly metabolize phenylalanine (Phe) resulting in its accumulation to neurotoxic levels. An early neurodevelopmental assessment and identification of risk factor for a lower cognitive performance could identify patients at risk of adverse outcomes. In our study, we compared PKU patients with a low vs high performance at the Griffith's Mental Development Scales (GMDS) at age 6 with the aim of identifying factors that predict their performance on this neurodevelopmental test.

Retrospective analysis of 89 PKU patients followed since 1992 was performed at Centro de Genética Médica Jacinto Magalhães, Porto, Portugal. PKU patients were stratified in low vs high performance in the GMDS 6 (cut-off= 88) and their features were compared: the ranksum was performed for continuous variables and for binary and categorical variables the Pearson's chi-square or Fisher exact test were performed (the latter for variables with cell count equal or lower than 5). Annual blood Phe measurements were used to classify metabolic control. A multivariable logistic regression was computed with a top-down strategy to predict low vs high GMDS6 performers. The ROC curves of regression models with Phe measurements at different ages were compared by the DeLong Method. Median Phe cut-offs were defined with the Youden's method. The GMDS 6 was correlated with the performance in the Wechsler Intelligence Scale for Children – Third Edition (WISC - III) at later ages by a linear regression; and schooling outcomes and unemployment were compared between GMDS6 low vs high by the Fisher exact test.

Fourteen patients were allocated to the low GMDS6 (GMDS6<88) group and 74 patients to the high GMDS6. The PKU patients with a low GMDS6 were born in earlier years (p= 0.008); had higher chances of having a more severe form of PKU (hyperphenylalaninemia vs mild PKU vs classic PKU, p= 0.047) and higher levels of Phe before treatment (p= 0.032) and at age 3 (p= 0.001). A multivariable logistic regression analysis was designed to predict low vs high GMDS6 adjusting for the log Phe values at age 3 and year of birth. The log Phe levels age 3 showed to be an independent predictor in this model. In addition, it was determined that a Phe levels cut-off of 7.8 mg/dL at age 3 can predict the PKU patients with low vs high GMDS6 (sensitivity= 72.6%, specificity= 78.6%). The performance on the GMDS6 was associated with the performance at the WISC-III at later ages (r=0.69, p<0.001) and schooling outcomes, but not with unemployment (p=0.216).

The PKU patient's performance on the GMDS6 is dependent of multiple modifiable and non-modifiable factors. Metabolic control under 6 years of age is a valuable predictor of the neurodevelopmental performance at that age and patients with higher Phe levels before age 6 might need a more personalized management.

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P.05 - Determination of Reference Values for 17-Alpha-Hydroxyprogesterone in Very Low Birth Weight Premature Infants

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Congenital adrenal hyperplasia is an autosomal recessive hereditary disease, caused by the deficiency of several enzymes implicated in the cortisol biosynthesis.

This disease is not included in the Portuguese newborn screening panel, and a determination of the parameter 17-alpha-hydroxyprogesterone is only done in the presence of sexual ambiguity or clinical suspicious of congenital adrenal hyperplasia.

In our country, every day, around 10% of very low birth weight premature infants (<1500 g) or less than 30 weeks gestation are born. These very premature babies have a deficiency in the hormonal development, which may cause false positive results in the evaluation of that parameter.

During the last year, 308 dried blood spot samples from newborns with low birth weight or less than 30 weeks gestation were analysed for 17-alpha-hydroxyprogesterone using Delphia® (PerkinElmer) method. The reference values for 17-alpha-hydroxyprogesterone determination were determinate from the 95 and 99 percentiles.

The premature newborns were stratified according to the birth weight. The data of this study allowed to established new reference values for low birth weight that should be higher than those that are used for the preterm and term neonates.

The aim of this work was to establish reference values for the determination of 17-alpha-hydroxyprogesterone in very low birth weight premature infants in order to exclude false positive results, for the diagnosis of congenital adrenal hyperplasia.

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P.06 - The Trimodular Haplotypic RCCX with c.955C>T Variant in a 21-Hidroxilase Deficiency Healthy Carrier

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Congenital adrenal hyperplasia (CAH, OMIM #201910) due to 21-hidroxilase deficiency (21-OH) is an autosomal recessive disorder caused by mutation in CYP21A2 gene. This gene is located on chromosome 6p21.3, closely adjacent with three other genes (STK19, C4 and TNX), forming a multiallelic copy number variation (CNV) module termed RCCX. This complex structure is highly prone to genomic instability which indirectly manifests in CAH diagnosis. The c.955C>T (p.Q319*) mutation of the CYP21A2 gene is a well-recognized case of this diagnosis complexity.

The authors report a 5 years-old girl with premature pubarche and thelarche which molecular testing of CYP21A2 gene revealed compound heterozygosity for c.1360C>T (p.P454S) and c.844G>T (p.V282L) mutations, compatible with 21-OH non-classic form. Genetic testing of her parents by Sanger sequencing allowed the identification of a heterozygous c.1360C>T (p.P454S) mutation in the father and a compound heterozygosity for c.844G>T (p.V282L) and c.955C>T (p.Q319*) mutations in the mother. Mother's endocrinological examination didn´t reveal signs of hyperandrogenism, delayed menarche or menstrual irregularities. Hormonal investigations were also normal. Further investigation on mother's genotype was made using Multiplex Ligation-dependent Probe Amplification (MLPA) for CNV detection.

Patient's mother carried the c.*12C>T variant in cis with c.955C>T mutation, which is a hallmark of a complex allele carrying two copies of the CYP21A2 gene - RCCX. MLPA analysis confirmed the duplication of the gene.

The majority of individuals with c.955C>T mutation have a duplicated functional CYP21A2 gene. Individuals who carry this mutation on one of the duplicated CYP21A2 genes and a pathogenic mutation on the other allele are not affected with CAH. A recent study reported a moderately frequent (2%) trimodular haplotypic RCCX structure with c.955C>T mutation and a second CYP21A2 bearing a specific c.*12C>T variant, in c.955C>T European carriers with normal steroid levels. In our case, the mother is a healthy c.955C>T carrier with this trimodular structure with a duplicated CYP21A2 with the c.*12C>T variant. This supports the idea that this variant could help in the genetic interpretation of c.955C>T mutation.

Duplication of the CYP21A2 gene should be suspected when the clinical and hormonal findings do not support the genetic diagnosis, particularly in individuals with c.955C>T mutation. The discrimination between a c.955C>T variant in single-gene copy alleles from the non-deficient variant in gene-duplicated alleles is important to clarify the diagnosis and to offer proper genetic counselling. The identification of the c.*12C>T variant could be a suitable marker to distinguish pathogenic and non-pathogenic cases in c.955C>T mutation context and improve the diagnosis of CAH.

POSTERS | POSTERS

P.07 - Turner Syndrome Mosaicism with Two Cell Lines: 45,X and Xp Deletion in a Female with Very Short Stature and Secondary Amenorrhea

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Turner Syndrome (TS) is the most common chromosomal aneuploidy and a well defined disorder, characterized by short stature, gonadal failure and some typical phenotypic features. About 50% of patients with TS have complete loss of one X chromosome (monosomy X), the rest of them, present mosaicism or structural abnormalities of the X chromosomes, such as, 46,X,r(X), 46,X,i(X), 46,X,del(X), among others. As complete monosomy X causes features of TS, the same phenotype is expected in cases with partial deletions of either the short or long arm of the X chromosome.

We present a female aged 50 referred for cytogenetic studies at 48, whose clinical indication was very short stature and secondary amenorrhea (at 33 years of age - early menopause). The karyotype revealed the presence of two cell lines: mos 45,X[8]/46,X,del(X)(p22.2)[22].

The presence of these two cell lines, may cause a great phenotypic variability including short stature, which is a common feature in females with this type of mosaicism. A 45,X cell line present in the gonads may explain ovarian failure at an early age. Various studies have been carried out in order to delineate and establish the proposed loci for some genes, relating to the TS phenotype. Some authors have indicated that the genes for physical and cognitive features lie on the short arm of the X chromosome, whereas genes for ovarian function are present on both the short and the long arms (Xp and Xq), respectively). The authors will establish the genotype/phenotype correlation between the patient and similar cases reported in the literature.

POSTERS | POSTERS

P.08 - Maturity-Onset Diabetes of the Young (MODY): Clinical and Genetic Spectrum

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The Maturity-Onset Diabetes of the Young (MODY) includes a heterogeneous group of monogenic diseases characterized by early-onset pancreatic beta cell dysfunction and autosomal dominant inheritance. MODY 2 and 3 subtypes are the most frequent, resulting from mutations in the glucokinase (CGK) gene and hepatocyte nuclear factor 1-alpha (HNF1A) gene, respectively, and present a distinct clinical phenotype. The aim of this study was to characterize the clinical, laboratory and genetic spectrum of a cohort of patients diagnosed with MODY.

A retrospective review of the clinical processes of patients with MODY admitted to the Pediatric Endocrinology department of a university hospital was conducted.

The 10 patients evaluated presented mild asymptomatic hyperglycemia in an occasional analytical study. Only one patient presented obesity. The mean age of detection of diabetes was 7 years (minimum 1 year, maximum 11 years) and 50% of patients were male. The mean hemoglobin A1c (HbA1C) at diagnosis was 6.3%. All patients had a family history of diabetes mellitus or hyperglycemia. The genetic study allowed confirmation of the diagnosis of MODY type 2 in nine patients and MODY type 3 in one patient. Dietary measures were instituted in all patients and was initiated sulphonylurea therapy in the patient with MODY type 3.

MODY type 2 is characterized by non-progressive mild hyperglycemia and low risk of complications and do not generally require any treatment. In contrast, in MODY type 3 progressive deterioration of glycemic control occurs, complications are frequent and their development is related to the degree of metabolic control and most of these patients require pharmacological treatment with sulfonylureas. The genetic study helped to predict the clinical course of the disease and guide the most appropriate management in a particular patient, including pharmacological treatment. Furthermore, it has important implications for the family as it enables genetic counseling and frequently triggers extended genetic testing in other diabetic family members, whose diabetes may eventually be reclassified.

POSTERS | POSTERS

P.09 - Silver-Russel Syndrome – Report of Two Cases

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Silver-Russell or Russell-Silver Syndrome (SRS) is an imprinting disorder characterized by prenatal retardation (birth weight two SD or more below the mean) and postnatal growth retardation (two or more SD below the mean for length or height), relative macrocephaly, fifth finger clinodactyly and typical facial features. Excessive sweating, changes in pigmentation, limb asymmetry, feeding and learning difficulties or global developmental delay (DD)/intellectual disability (ID) usually mild, may be present. The final mean height is 151.2 cm in men and 139.9 cm in women. Other important issues are gastrointestinal disorders, recurrent hypoglycaemia, insulin resistance, premature adrenarche, early puberty and bone age delay. It is a genetically heterogeneous condition, caused in 30-60% of cases by hypomethylation of the paternal imprinting center (IC1) on chromosome 11p15.5. This change in methylation pattern results in reduced paternal IGF2 expression, leading to growth restriction. About 5-10% of individuals have maternal uniparental disomy of chromosome 7 (UPD7). In about 40% of cases the cause of SRS is unknown, so called idiopathic SRS.

Clinical files were reviewed in order to describe two patients with a clinical diagnosis of SRS. Two boys aged 1 and 6 years. They presented severe intrauterine growth restriction, low birth weight and height (below 3rd percentile), failure to thrive (progressing below the 5th percentile for weight and length) and characteristic dysmorphic features (relative macrocephaly, triangular face, prominent forehead and fifth finger clinodactyly). Both boys had decreased body mass, feeding difficulties needing nutritional supplementation, and motor delay. The oldest boy also had speech delay but cognition was normal in both.

Hypomethylation of the IC1 region was detected in both cases. They were referred for endocrinological evaluation and follow-up. The older boy is receiving treatment with growth hormone (GH) and GH is also being considered in the younger one.

SRS is primarily a clinical diagnosis, but molecular testing allows its confirmation.

SRS should be considered in the differential diagnosis of short stature of prenatal onset.

The management of children with SRS requires a multidisciplinary approach due to multiple system involvement.

Treatment with GH is useful and indicated in SRS. It might increase linear growth. GH also improves body mass and appetite, reducing the risk of hypoglycaemia, and has a positive impact on psychomotor development.

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P.10 - Neurocognitive Outcome and Personality Profile of 28 PKU Adult Patients Followed-up at CGM-CHP: A Retrospective Study

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Phenylketonuria (PKU, OMIM 261600), is a rare inherited autosomal recessive disorder characterized by a deficiency in the phenylalanine hydroxylase enzyme necessary for the conversion of the amino acid phenylalanine (Phe) to tyrosine. Untreated PKU results in increased brain Phe levels, decreased tyrosine brain influx, and reduced cerebral protein synthesis. Neurocognitive functioning and psychological disturbances have been reported in patients with PKU. A slight decrease in intellectual quotient (IQ) together with impairments on the executive function and neuropsychiatric comorbidities may persist in treated patients. The main aim of this study was to characterize some adult PKU patients in terms of their neurocognitive outcomes and personality traits that may interfere with adaptation to different tasks in their daily life.

We studied 28 patients detected in Newborn Screening (18 female, 10 males) aged 18–36 years (mean=26.7, sd=5.02). We considered the quality of dietetic control (QDC), defined as the annual medians of Phe, as independent variable. The treatment outcome was evaluated considering last IQ as a global value (Intellectual Wechsler Adult Scales) and the subtest profile. The personality profile was evaluated using the Sixteen Personality Factor Questionnaire (16 PF-5). We also considered the level of school education attained and their professional career.

PKU patient's global IQ mean was lower than standard values, with a mean of 95.3±18.3 [57-121] revealing subtle disabilities. A specific profile of neurocognitive and behavioural difficulties was found in these patients. These difficulties were negative correlated with the QDC and did influence their school progress, professional success and treatment adherence. Results on 16PF-5 showed low values on scales evaluating social boldness, extroversion and reasoning. High values were found on scales evaluating vigilance, apprehension and self-reliance. On global dimensions, they scored above the mean on anxiety and below mean on extraversion.

Our results showed a specific neurocognitive profile and some personality traits in these adult PKU patients that allow a better understand of the difficulties in their psychosocial behaviour suggesting the need of a special psychological support throughout life.

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P.11 - A Case of Klinefelter Syndrome with Multiple Cell Lines

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Klinefelter Syndrome (KS) is the most frequent sex chromosomal disorder in men occurring in about 1:600 newborn male and diagnosed in 11% of azoospermic men. KS is characterized by the presence of a supernumerary X chromosome (47,XXY), being the usual normal male karyotype 46,XY. KS patients are characterized by hypogonadism, gynecomastia, azoospermia (or oligospermia), high levels of gonadotropins, tall stature, small testes, broad hips and hormonal disorders. In KS, 47,XXY karyotype represents 80-90% of the cases; the remaining 10-20% cases are described as higher-grade aneuploidies (e.g. 48,XXXY) or mosaicisms (e.g. 47,XXY/46,XY).

The authors present a case of KS mosaicism with four cell lines. A man aged 37 years was referred for chromosomal studies, presenting primary infertility, small tests, history of bilateral cryptorchidism and azoospermia. The endocrinological analysis revealed increased folicule stimulating hormone (FSH) and low testosterone levels. The karyotype was mos 47,XXY[95]/46,XX [2]/49,XXXXY[1]/46,XY[4].

Mosaicisms involving more than three cell lines are rarely found, have several endocrinological alterations and the most frequent cell line may be distinct among different patients. Previous studies showed that in cases diagnosed as KS mosaicism the severity of the clinical features is variable since it depends on the number of additional X chromosomes, the number of abnormal cells and their location in the body tissues. Usually Klinefelter mosaics with only two cell lines (e.g. 47,XXY/46,XY) result in less evident and severe clinical symptoms and X polysomies (e.g. 48,XXXY) in more severe phenotypes.

Phenotype of KS is still not completely understood mostly due to the large number of KS patients that remain underdiagnosed (only 25% of the expected number of patients is properly diagnosed) being the majority detected during adulthood. The ability to perform an early diagnose might prevent any educational and psychological difficulties. Furthermore, these studies play a key role on the fertility counselling through the accurate frequency of abnormal cells. Hence, the authors enhance the importance of the diagnosis of these variants in relation to the classical KS phenotype improving the clinical management and genetic counselling of these patients.

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POSTERS

P.12 - Chromosome 18q Deletion Syndrome - A Rare Genetic Cause of Short Stature

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Short stature, defined as height of <0.4th centile, may have several ethiologies, mainly, familial or constitutional short stature, chronic diseases, maternal infections or genetic causes. The 18q deletion syndrome (OMIM #601808) is highly variable (both in phenotype and chromosomal region involvement), but mainly characterized by developmental delay/mental retardation, short stature, hypotonia, hearing impairment, facial dimorphisms, and others. Since the work from Cody et al., short stature with growth hormone insufficiency has been associated with this deletion.

We present a case diagnosed by the Neurodevelopmental team at a peripheral hospital.

Sixteen years-old boy has been followed at Neurodevelopmental outpatient clinic due to mild developmental delay and learning difficulties. He is the sixth and last child of healthy non-consanguineous parents, without relevant family history. He had history of recurrent respiratory infections and a minimal apical interventricular communication. At our consultation, he presented with proportionate short stature (<<P5), sexual developmental delay, mild unspecific dysmorphisms and minor skeletal alterations.

The cognitive evaluation showed a global IQ of 53. Wrist x-ray revealed a 6 years delay on bone age. Mid-parental height was 165cm (P5). Hormonal study showed IGF BP-3 3,22 mg/L, IGF-1 91 ng/mL, Delta-4-androstenediona <0,3 ng/mL, free testosterone 0,36 pg/mL. Both karyotype and fragile X syndrome study, as well as brain MRI, were normal.

Lastly, array-CGH revealed a deletion of 2,2 Mbp at 18q23 region, involving 13 genes, confirming the diagnosis of 18q deletion syndrome.

At Genetic consultation, FISH study confirmed the deletion in the boy and was negative for his mother. It was not possible to study his father, as he did not attended Genetic consultation.

The boy is being on follow-up at neurodevelopmental and endocrinology consultations and he will return to genetic consultation before reproductive project.

With this work, the authors intend to stress the need to investigate the genetic etiology of children with global development delay associated with short stature and sexual developmental delay. Treatment with hormonal substitution has been described with a good outcome. A multidisciplinary team is always essential, including the genetic consultation for understanding the proper follow-up for the syndrome and genetic counselling of the patient and family.

POSTERS | POSTERS

P.13 - Lysosphingomyelin-509 Plasma Quantification – A New Era in Niemann-Pick type C (NPC) Diagnosis in Portugal

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Niemann-Pick type C (NPC) disease (OMIM#257220; OMIM#607625) is a neurodegenerative disease with an autosomal recessive pattern of inheritance characterized by mutations in either the NPC1 or NPC2 genes. Mutations in these genes cause an abnormal endosomal-lysosomal traffic leading to lipids accumulation in the acidic compartment of lysosomes/ late endosomes. Heterogeneous clinical presentations, with a wide range of nonspecific symptoms, are motive of harder and delayed diagnosis. Until now, filipin staining of cultured skin fibroblasts has been considered the qualitative biochemical gold standard method.

Among sphingolipids accumulated in NPC patients a slight increase of lysosphingomyelin (LysoSM) and a higher increase of its carboxylated analogue, lysosphingomyelin-509 (LysoSM-509) were already reported in plasma. Furthermore, LysoSM and LysoSM-509 are also increased in acid sphingomielinase deficiency affected patients (ASMD- formerly known as Niemann-Pick type A/B). However LysoSM seems to be 10 times higher in ASMD than in NPC patients.

The aim of this work was to develop a simple straight forward method to quantify LysoSM and LysoSM-509 in plasma of NPC suspected patients.

Using an in-house LC-MS-MS developed method to quantify NP disease biomarkers, we tested, as a proof of concept, plasma from 18 NPC (10 infantile and 8 adult) and 11 ASMD diagnosed patients, as well as 7 NPC obligate carriers, along with a control population.

NPC patients revealed a LysoSM-509 and LysoSM concentration range of 293-9223 and 13.3-32.6 µmol/L, respectively. ASMD presented a LysoSM-509 and LysoSM concentration range of 2984-17082 and 258-527 µmol/L, respectively. Although ASMD patients revealed higher LysoSM-509 concentration, correlation analysis of both lyso forms allows discrimination between NPC, ASMD and controls. Correlation analysis of carrier's concentration of both lyso forms does not differ from the obtained in control population.

LysoSM and LysoSM-509 quantification in plasma is a cutting-edge LC-MS/MS method that proved to be a reliable screening approach for NPC suspected patients, overcoming individual filipin staining test interpretation.

Moreover, this method allows diagnose of NPC and ASMD in a single run, in a low invasive sample collection, avoiding highly expensive and time consuming techniques and reducing diagnostic delay.

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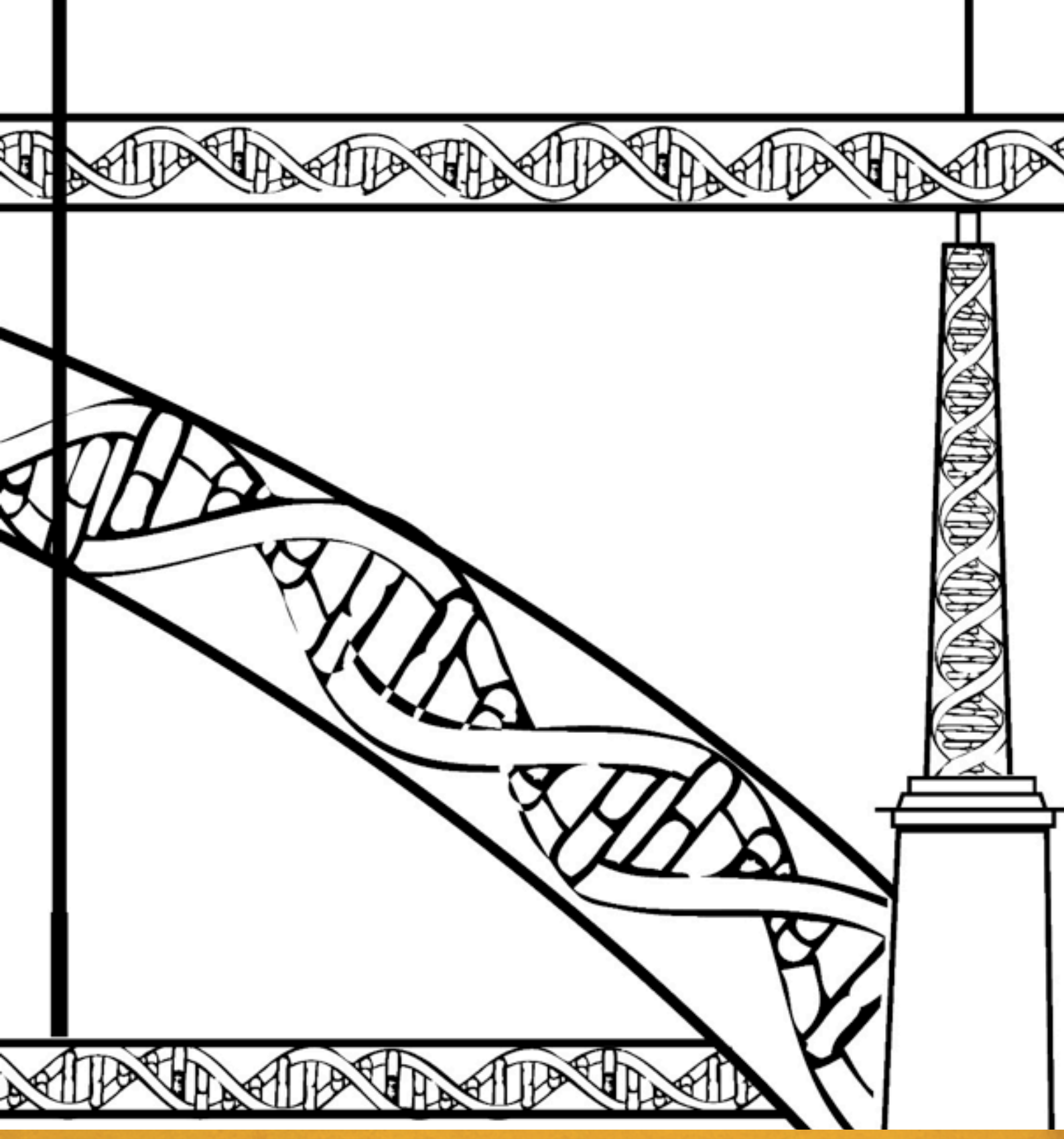

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