SINTOMI NEUROLOGICI IN MALATTIE METABOLICHE RARE

Clinical Round
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D.A.G 3 anni e 3 mesi
Ricovero (settembre 2020)

- Ritardo del linguaggio
- Alimentazione selettiva
- Stereotipie motorie

Anamnesi perinatale muta
APR: agenesia renale sx congenita

EON: nella norma
CC 51 cm (75°p)
altezza 90 cm (3°p) peso 14,2 Kg(25-50°p)
epicanto bilaterale e ipertelorismo

Procedure diagnostiche

- Esami ematochimici ed esame urine: nella norma
- ECG ed ecocardiogramma: nella norma
- Ecografia addome: monorene dx
- EEG: sharp waves centro-temporali bilaterali e rare scariche generalizzate di punta onda atipiche
- BAEP: nella norma
- Valutazione neurooftalmologica: nella norma
- Valutazione cognitiva (Scala Leiter-R): QI 68
- Vineland II: competenze adattive moderatamente basse
- Valutazione logopedica: Conferma ritardo linguaggio espressivo
- Consulenza genetica: analisi esoma mediante NGS

Diagnosi alla dimissione: Ritardo globale di sviluppo con maggior compromissione linguaggio espressivo
**Variante in emizigosi sul cr. X nel gene MAOA**

C.410 A > G (p.Glu137Gly) Missense mutation

Deficit monoamina ossidasi: difetto del metabolismo delle amine

**Metaboliti:**
- **5-HIIA** 0.6 mg/24h ridotto
- **VMA** 0.2 mg/24h ridotto
- **HVA** ai limiti inferiori

**Metanefrine urinarie:**
- **Normetanefrinine** aumentata
- **Metanefrina** ai limiti inferiori
- **Serotonina** nella norma

**Serotonina (siero):** 6025 nmol/L (v.n. 138-1080)
**X-Linked Borderline Mental Retardation with Prominent Behavioral Disturbance: Phenotype, Genetic Localization, and Evidence for Disturbed Monoamine Metabolism**


**SÍNDROME DI BRUNNER**

mild mental retardation, abnormal behavior

- The locus for this disorder could be assigned to the Xp11-21 by linkage analysis
c.886C>T; p.Q296*Truncating mutation

- Results of 24-h urine indicated a marked disturbance of monoamine metabolism These data are compatible with a primary defect in the structural gene for MAOA

**20 ans après: a second mutation in MAOA identified by targeted high-throughput sequencing in a family with altered behavior and cognition**

Amélie Piton,*1,2,10, Hélène Poquet3,4,10, Claire Redin1,3, Alice Moreau3, Julia Lauer3, Jean Muller1,9, Julien Thevenon3,4, Yvon Herengre5, Sophie Chancenot9, Marlène Bonnet7, Jean-Michel Pinot1, Frédéric Huët1, Christel Thauvin-Robinet3,6, Anne-Sophie Jaeger1, Stéphanie Le Gras8, Bernard Jost8, Bénédicte Gérad1, Katell Pech8, Jean-Marie Launay4, Laurence Faivre5,10 and Jean-Louis Mandel1,2,3,10

The identification of c.797_798delinsTT; p.C266F Missense mutation confirms, for the first time since 1993, the monogenic implication of the MAOA gene in ID, autism and behavioral disturbances
MAOA<sub>A863T</sub> KO mice are the first murine line with a naturally occurring nonsense mutation of MAO A gene.

The similarity of this mutation to the human condition makes this line of mice a valuable tool for translational research, and further exploration of the role of this enzyme on brain function and behavioral regulation.

Studies in mammalian models are particularly meaningful, given the high homology of human MAOA with those of other placental mammals.

The convergence of human and animal research is proving helpful to our understanding of how MAOA influences antisocial and violent behavior.

MAO A deficiency results in a spectrum of intellectual disability and socio-communicative deficits, which encompass both antisocial behavior and ASD(Autism spectrum disorder)-like features.
Cautious treatment with a SSRI and dietary modifications can improve symptoms.

III.4 – IV.5 – IV.6 50 mg/day of sertraline very slowly increased
- initial exacerbation of serotonergic symptoms
- then III:4 and IV:5 (the more severely affected individuals) reported reduction in the frequency of symptoms
- normalisation of biochemistry was demonstrated on treatment with sertraline

Cautious treatment with a SSRI and dietary modifications can improve symptoms.
Sertraline is OFF-LABEL <18 years

It can be taken by children aged 6 to 17, ONLY for obsessive compulsive disorder (OCD).

- The usual dose of sertraline in children aged 6 to 12 is 25mg a day (but this may be increased to 50mg a day after a week)
- The usual dose of sertraline in children aged 13 to 17 is 50mg a day.
Children aged 6 to 17 might have their dose increased up to 200mg a day, if needed.

There is supportive animal model data that administration of the SSRI fluoxetine reduces aggressive behaviour and perseverative responses in MAOA knockout mice and improves social deficits and perseverative responses in mice with a hypomorphic MAOA variant.

Earl and Cheung, who originally recommended a therapeutic trial of SSRI in Family R, postulated that symptoms related to serotonergic excess would be reduced over time because of reduction of peripheral serotonin.

Blood serotonin levels fall in individuals treated with SSRI’s due to inhibition of platelet serotonin transporters, platelets being the major storage site of serotonin in the blood.
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<td>Borderline to mild Intellectual disability</td>
<td>Variable intellectual disability</td>
<td>Mild intellectual disability ADHD. Family H: <strong>3 affected adults males</strong></td>
<td>Mild intellectual disability</td>
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<td><strong>14 affected adults males</strong></td>
<td><strong>2 affected adults males</strong> 1 child (7 years)</td>
<td><strong>Family H: 3 affected adults males</strong></td>
<td><strong>1 child (3 years)</strong></td>
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<td>Repeated episodes of aggressive and violent behaviour, associated with night terrors.</td>
<td>Autism spectrum disorder. Auto- and hetero-aggressive behaviours Hand stereotypies</td>
<td>History of impulsivity and aggressive outbursts with high tyramine foods Severe nightmares in childhood and adolescence <em>Flushing/diarrhoea/ headache Symptoms (treated with SSRI)</em> Essential tremor</td>
<td>Simil autism spectrum disorder Hand stereotypies</td>
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<td>High serotonin and normetanephrine, low HVA, VMA, 5-HIAA</td>
<td>High metanephrine and normetanephrine, serotonin not tested, low VMA, 5-HIAA</td>
<td>High serotonin and normetanephrine</td>
<td>High serotonin and normetanephrine, low VMA, 5-HIAA</td>
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Discussione

**Sindrome di Brunner**

Nel nostro pz dalla data del ricovero comparsa di: irritabilità, agiti eteroaggressivi, ipersudorazione e iperattività

- Prospettive terapeutiche (utilizzo SSRI ed implicazioni etiche)
- Comunicazione diagnostica
- Ulteriori indagini anamnestiche ed eventualmente genetiche ai familiari
- Follow up → ADHD, aggressività, disturbi del comportamento in età adolescenziale e adulta
Grazie per l’attenzione