Brain MRI Abnormalities and Genetic Results in a Series of 30 Patients With Congenital Isolated Hypogonadotropic Hypogonadism (CIHH).

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Background. CIHH is a genetic syndrome that combines reproductive and brain abnormalities. Up to now, the brain phenotype has not been well characterized.

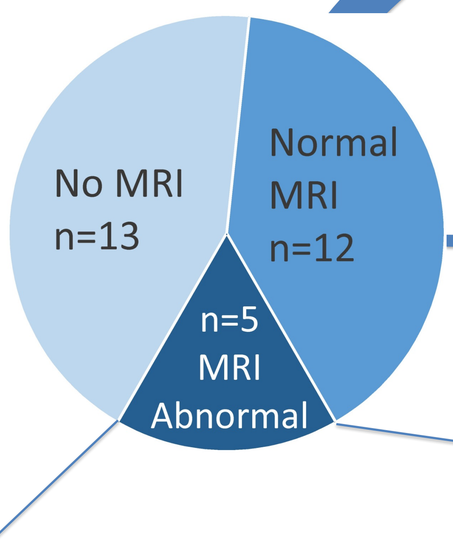
Methods.

- Investigation of a series of 30 patients presenting a CIHH.
- Panel of 16 genes related to hypogonadotropic hypogonadism (HH) by next generation sequencing on a MiSeq® Instrument (Illumina) and by using a validated targeted approach with xGen® Lockdown® Probes (IDT).
- In a second time the cohort was reviewed to search about cerebral anomalies or hypothalamic-pituitary malformations, based on the magnetic resonance imagery (MRI).

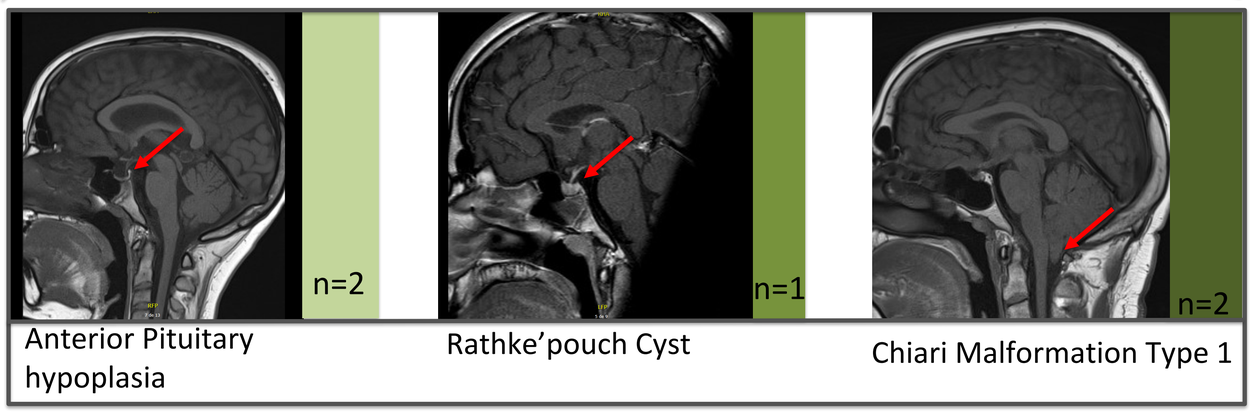
Total of individuals	(n=30)
Mean age (years)	30,2 (n=30)
Anosmia	5 (n=26)
Dysmorphic features	2 (n=30) (for the 2 patients : clef palate)
Consanguinity	2 (n=26)
Familial case	8 (n=28)
Ethnicity	(n=22)
Caucasians	14
Others	8

AIM
Study of the **neuroradiological and genetic features** in the cohort Of CIHH

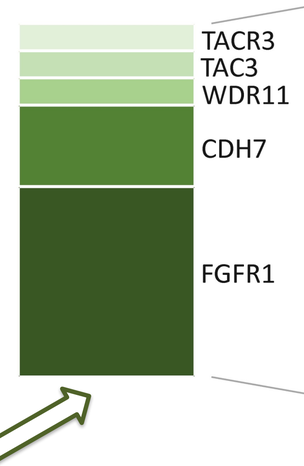
Brain MRI in the cohort (n=30)

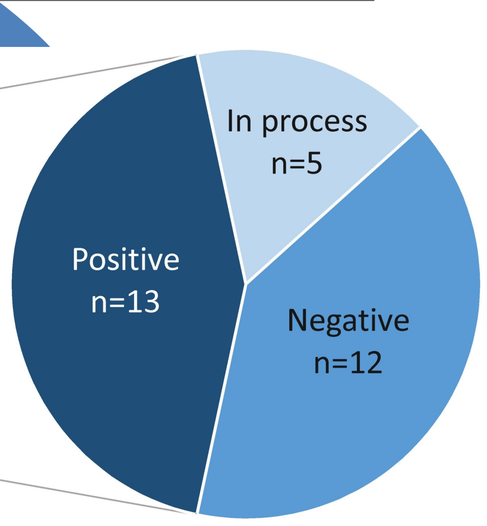


n=6 heterozygous for one pathogenic variant
-FGFR1: c.1663+1G>A, class 5
-WDR11: c.3450 T>G,p.Phe1150Leu, class 4
New variants :
-TACR3 : c.170 C>T,p.Ala57Val, class 3
-TAC3: c.238+1 G>A, class 5
-FGFR1 : c.169C>A,p.Leu57Met, class 3
-CDH7 : c.7212_7214del,pArg2405del, class 3



Genetic results in the cohort (n=30)





n=1
Heterozygous for **a new pathogenic variant**:
FGFR1 c.1025T>A; p.Leu342*

Discussion.

Incidence.

In our cohort, Chiari malformation type 1 (CM1) was found in 2 of the 17 patients (12%) who performed a brain MRI. In the general population, incidence of CM1 was estimated at 0,7%.

CM1 is known to be associated with a series of genetic syndrome (1,2). A cohort of patients with Costello syndrome is reported with higher incidence of CM1 (17%). In this report, interestingly, among the three patients with Costello syndrome and CM1, two were described with a hypogonadism.(3)

In the endocrinology field, it was currently reported that 5 to 20% of patients with isolated growth hormone deficiency (GHD) or multiple hormone deficiency (MPHD) presented a CM1. (4)

Etiology of CM1.

Theory of breech delivery was evocated in the past years (CM1 caused by traction of the spinal cord during breech delivery). But further observations disproof this mechanism.(4)

Currently, the etiology remains unclear and CM1 is most likely multifactorial. Genetic contribution is argued by familial aggregation and twin studies. Studies with animal models and human morphometric analyses have suggested a mesoderm insufficiency.(5,2,6)

The abnormal development of the cerebellar tonsils occurs during the fourth to eighth first weeks of gestation, a critical period for the formation of the hypothalamo-pituitary region. This fact contributes to support the theory of a defect during the embryogenesis.(4)

A case-control association study of 58 developmental genes was published in 2013.(6) The investigated genes were involved in somitogenesis, placental angiogenesis, sclerotome development or CM1-associated syndromes. Common variants in 14 genes out of the 58 initial genes are though to confer a susceptibility to CM1, among this 14 genes FGFR1 was reported.(6)

In our cohort, genetic analyses revealed a new *FGFR1* mutation for one of our patient with CM1. This interesting result establish for the first time a correlation between CM1 and *FGFR1* mutation in a context of CIHH.

Conclusion. For the first time, we suggest a new syndromic association between CIHH and CM1. Larger series are needed to extend the phenotype and the genotype of these patients. The role of FGFR1 is an hypothesis who should be more investigated.

References
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