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PII: S1769-7212(12)00157-7

DOI: 10.1016/j.ejmg.2012.04.010

Reference: EJMG 2682

To appear in: *European Journal of Medical Genetics*

Received Date: 15 December 2011

Accepted Date: 11 April 2012

Please cite this article as: G. Terrone, A. D'Amico, F. Imperati, M. Carella, O. Palumbo, M. Gentile, R.B. Canani, D. Melis, A. Romano, I. Parente, M. Riccitelli, E. Del Giudice, A further contribution to the delineation of the 17q21.31 microdeletion syndrome: Central nervous involvement in two Italian patients, *European Journal of Medical Genetics* (2012), doi: 10.1016/j.ejmg.2012.04.010.

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A further contribution to the delineation of the 17q21.31 microdeletion syndrome: central nervous involvement in two Italian patients

Gaetano Terrone[1]*, Alessandra D'Amico[2], Floriana Imperati[1], Massimo Carella[3], Orazio Palumbo[3], Mattia Gentile[4], Roberto Berni Canani[1], Daniela Melis[1], Alfonso Romano[1], Iolanda Parente[1], Marina Riccitelli[1], and Ennio Del Giudice[1]

[1] Department of Pediatrics, Federico II University, Naples, Italy

[2] Department of Radiology, Neuroradiology Unit, Federico II University, Naples, Italy

[3] Department of Human Genetics, IRCCS "Ospedale Casa Sollievo della Sofferenza", San Giovanni Rotondo, Foggia, Italy

[4] Department of Medical Genetics, Di Venere Hospital, ASL Bari and IRCCS "Saverio De Bellis", Castellana Grotte, Bari, Italy

*Corresponding author at: Department of Pediatrics, Federico II University, Via Pansini n°5, Naples, Italy.

Email: gaetanoterrone@virgilio.it

Abstract:

The 17q21.31 microdeletion syndrome is a genetic disorder characterized by intellectual disability, facial dysmorphisms and a typical behavioral phenotype. Patients are usually described as friendly and cooperative but they can also show behavioral problems such as hyperactivity, bad humor, temper tantrums and poor interaction. Central nervous system involvement includes callosal dysgenesis/absence, enlargement of lateral ventricles and abnormalities of cyngulate gyrus. We report on two Italian patients with the 17q21.31 microdeletion syndrome better emphasizing neuroimaging and neuropsychological characteristics. In particular, we carried out an assessment of intellectual efficiency and behavior that turned out to be within the mild-moderate range of mental retardation, as already reported in the literature. To the best of our knowledge this is the first report of a patient with the 17q21.31 microdeletion and a Chiari malformation type 1 coexisting with a mild anomaly of medulla oblongata. This malformation should be considered in patients with the 17q21.31 microdeletion syndrome, presenting suggestive symptoms (headache, neck pain, cerebellar signs or muscle weakness).

Keywords: 17q21.31 microdeletion syndrome, Arnold-Chiari type 1 malformation, behavioral disorders, *MAPT* gene.

1. Introduction:

During the last few years, using high resolution genome analyses, several new microdeletion syndromes have been identified in patients with intellectual disability of unknown etiology and mild dysmorphisms, including, for example, the recurrent deletion involving chromosome region 17q21.31. [1,2]. Array-CGH analysis also allowed to reveal microduplication of the 17q21.31 region, associated with a clinical phenotype milder than those seen in the microdeletion counterpart [1]. The prevalence of the 17q21.31 microdeletion syndrome is 1 in 16000, while, to the best of our knowledge, only six cases of the 17q21.31 microduplication have been described in literature up till now [1,2]. Although a specific pattern of phenotypic anomalies has been described, the 17q21.31 microdeletion syndrome is still underdiagnosed.

The critical region deleted in this syndrome spans about 424 kb, encompassing at least six genes, *C17orf69*, *CRHR1, SPPL2C, MAPT, STH*, and *KANSL1* [2]. Haploinsufficiency of one or more of these genes may underlie the phenotype seen in individuals with the 17q21.31 deletion syndrome. Recently, a smaller deleted interval (205 kb), encompassing only the *MAPT, STH* and *KANSL1* genes has been identified in a patient showing the classical 17q21.31 phenotype [3]. It is known that the deleted region, containing microtubule associated protein tau (*MAPT)* gene, coincides with an inversion polymorphism of about 900 kb [4]. Two highly divergent *MAPT* haplotypes, H1 and H2, with distinct linkage disequilibrium patterns across the region have been described [4,5]. The *MAPT* haplotype H2, relatively common in European populations, is linked to the recurrent deletion events associated with the 17q21.31 microdeletion syndrome [5]. The *MAPT gene* is also of particular interest, as it is highly expressed in brain and involved in several neurodegenerative diseases.

Clinical features of the syndrome include: developmental delay, intellectual disability, hypotonia, seizures, heart anomalies, renal/urologic anomalies, hypermetropia, deformities of the feet and/or spine, facial dysmorphisms (abnormal hair color/texture, high/broad forehead, ptosis, blepharophimosis, upward slanting palpebral fissures, epicanthal folds, large/prominent ears, tubular or pear-shaped nose, bulbous nasal tip, everted lower lip). Behavioral style is described as friendly, amiable and cooperative with or without frequent laughing, reminding of the phenotypic features of Angelman syndrome. However, behavioral problems including hyperactivity, bad humor, temper tantrums, poor interaction with other children and speech delay are also reported.

In the present paper, we report on neuroimaging and neuropsychological features of two Italian patients with the 17q21.31 microdeletion syndrome with a focus on their evolution in time.

2. Patients and methods

2.1 Case reports

Patient 1

This girl was born at term after an uneventful pregnancy and delivery from Caucasian non-consanguineous healthy parents with a birth weight of 2.630 kg (5th-10th centile). At birth, head circumference and length were 35 cm (50th centile) and 46 cm (5th-10th centile) respectively. Developmental delay, generalized muscle hypotonia and facial dysmorphisms were evident from infancy. In the first few months of life, she suffered from several episodes of laryngospasm induced by a hypoplastic epiglottis. Beginning from the age of 9 months, she had recurrent episodes of simple febrile seizures. An interictal sleeping electroencephalogram (EEG) revealed discharges of sharp waves in left temporal area. Because of a strong parental anxiety, she began a prophylactic treatment with phenobarbital. At the age of 8 years physical examination revealed some dysmorphic features including tubular ‘‘pear shaped’’ nose, bulbous nasal tip, strabismus, epicanthal folds, upward slant, low-set ears, congenital absence of some permanent teeth, malocclusion, large central diastema, thick hair, hirsutism on the back, cubitus valgus and kyphosis. She also showed many pigmentary skin changes such as four cafè-au-lait spots and several melanocytic nevi that reminded of those seen in patients with cardio-facial-cutaneous syndrome. However, karyotype, FRAX-A molecular test, FISH for Velo-cardio-facial syndrome (VCFS) gave normal results. Because of nocturnal and diurnal enuresis, she began a treatment with oxybutynin beginning from the age of 6. At 12 years she had a new tonic-clonic seizure in the absence of fever with an interictal EEG that confirmed sharp-waves in the left temporal area. Subsequently, seizures did not recur and phenobarbital treatment was gradually stopped at the age of 16. An echocardiogram at 14 years showed mild tricuspid and mitral insufficiency without pulmonary hypertension. A follow-up echocardiogram performed at 18 years confirmed a normal pulmonary pressure (PaP =21 mmHg). At the same age a visual acuity test and fundoscopic examination were normal.

Patient 2

This girl was the third child of Caucasian non-consanguineous healthy parents and was born at term after an uneventful pregnancy and delivery: birth weight was 3,300 grams (25th-50th centile), length 52 cm (75 th -90th centile) and occipito-frontal circumference 36 cm (75th centile). Developmental delay, significant hypotonia and joint laxity were apparent from the first few months of life. Karyotype was 46, XX. She received speech and psychomotor therapy from the age of 2 years. At that age, a sleeping EEG was normal. Because of speech delay, an auditory brainstem response at the age of 3 showed a normal threshold value in both ears (20 dB nHL in left; 30 dB nHL in right ear). At 6 years of age, her weight was 18.100 Kg (25 th centile), height was 111 cm (25th centile) and head circumference was 51 cm (50th centile). Echocardiogram and renal ultrasound did not show congenital anatomical defects.

2.2 Neuroimaging studies:

The examinations were performed with a 1.5 Tesla imager (Philips Medical System). The following brain sequences were performed: axial Flair; axial T2 TSE-weighted images; coronal IR T1-weighted; coronal T2 TSE-weighted images, integrated by an axial Single-Shot Echo-planar (EPI) Diffusion.

Sagittal TFE T1 weighted 3 D-weighted images subsequently reconstructed on axial and coronal planes were also used in both cases.

2.3 Neurodevelopmental studies:

In both patients we performed an evaluation of intellectual efficiency. The first patient was tested with the Wechsler Intelligence Scale for Children (WISC-R and WISC-III); while the second was tested with the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) [6,7]. Adaptive behavior needed for everyday living activities (communication, daily living skills and socialization) was tested with the Vineland Adaptive Behavior Scales (VABS). The first patient was also tested with the Schedule for Affective Disorder and Schizophrenia (K-SADS) to rule out psychopathological disorders [8,9].

2.4 SNP array analysis

The SNP array analysis was performed on probands and their parents. We used the Affymetrix Genome Wide Human SNP Array 6.0, which included over 906,600 single nucleotide polymorphisms (SNPs) and more than 946,000 probes for the detection of copy number variations. The median inter-marker distance taken over all 1.8 million SNP and copy number markers combined was less than 700 bases. Samples preparation, hybridization and scanning were performed using GeneChip® Instrument System hardware according to manufacturer's specifications.

In addition, the copy number and genotyping analysis were performed using Genotyping Console Software 4.1 (Affymetrix, Santa Clara, CA, USA).

2.5 MLPA/FISH analysis

To confirm deleted regions, a specific multiplex ligation-dependent amplification assay (MLPA) was performed on patient DNA samples using Salsa MLPA kit P275-B1 MAPT-GRN (MRC-Holland, Amsterdam, The Netherlands) that contained 13 probes for *MAPT* gene and 5 probes each for GRN (*PGRN*) and the *CRHR1* genes. In addition, it contained several probes for other genes in the 17q21 region, as well as 10 reference probes detecting different autosomal chromosomal locations. Only in the first patient FISH analysis was performed using four BAC clones (RP11-339E12, RP11-80L9, RP11-111I23 and RP5-843B9).

3. RESULTS

3.1 Neuroimaging studies:

In the first patient brain Magnetic Resonance Imaging (MRI), performed at 9 months, was normal. Other two brain MRIs were performed at 8 and 16 years respectively, and only showed a mild enlargement of some perivascular spaces of Virchow-Robin in the white matter, especially near the left peritrigonal area (Fig.3a), together with an asymmetry of the temporal horns in presence of normal volume and signal of the hippocampal structures (Fig.3b).

In the second case, the first brain MRI at 6 months of age showed some small hyperintensities of the periventricular white matter, while a subsequent one, at the age of 3 years, only exhibited dilatation of some perivascular Virchow-Robin spaces bilaterally located at the posterior white matter in absence of other signal abnormalities. A dysmorphic corpus callosum, characterized by hypoplasia of the splenium and rostrum with a thickening of the anterior part of the body and the genu, was evident (Fig. 4a). Consequent to the splenial hypoplasia there also was an additional abnormal orientation of the sulci of the posterior part of the cyngulate gyrus together with a mild enlargement and an abnormal morphology of the lateral ventricles. An incomplete gyration of the hippocampi was more evident on the right side, with consequent dilatation of the temporal horns (Fig.4b). An unusual prominence of the left olive over the surface of the medulla oblongata was also appreciable (Fig 4c-d). The low position of the cerebellar tonsils, 8 mm under the occipital foramen, allowed to diagnose a Chiari malformation type 1 (CM1) (Fig.4a). A follow-up brain MRI, performed at 6 years old, did not show any further changes.

3.2 Neurodevelopmental studies:

In the first patient, the WISC-R at the age of 8 years showed a Full Scale Intelligence Quotient (FSIQ) of 50 (verbal IQ=63, performance IQ=50). Retesting using WISC-III at age of 17 years confirmed a moderate intellectual disability with a FSIQ of 49 (verbal IQ=41, performance IQ=39). The VABS score of 41 was in line with the intellectual level, while she showed a performance level corresponding to a 5-6 year-typical-development. K-SADS did not show any signs of current psychopathology. She had a friendly disposition with difficulty in recognizing potentially dangerous situations.

In the second patient, the intellectual assessment with the WPPSI at the age of 5 years gave a FSIQ of 68 (verbal IQ=78, performance IQ=66) with a slightly delayed global intellectual functioning. Non verbal information processing was deficient, especially in the tasks of graphic and three-dimensional assemblage of differently oriented objects. This girl showed good linguistic skills with a functionally correct semantic-lexical and verbal production. However, the comprehension of complex sentences was delayed for age. Verbal expression included many dyslalias that occasionally impaired speech comprehension. Personal and social skills were appropriate to the development level attained. A lack of proactive behavioral style was appreciated with mutism and passive attitudes. A further clinical observation, performed at 6 years showed a slight improvement of linguistic and visuospatial skills. Fine motor and graphic reproduction skills were better than at the first assessment; however, a short sustained attention span was confirmed.

3.3 SNP array analysis

This study disclosed, in patient 1, a 17q21.31 deletion of 541 kb from CN_734865 (41,031,000 bp) to SNP_A-2156357 (41,572,099 bp) probes, which were the first and the last deleted oligonucleotide from the centromere, respectively. The proximal (centromeric) and distal array markers with normal ratio were CN_734864 (41,020,464 bp) and SNP_A-4304183 (41,575,332 bp) respectively, based on UCSC Genome Browser, (NCBI build 36, hg18).

In patient 2, the size of the deletion in 17q21.31 was of 504 kb from CN_734870 (41,065,935 bp) to CN_737156 (41,569,931 bp) probes, which were the first and the last deleted oligonucleotide from the centromere, respectively. The proximal (centromeric) and distal array markers with normal ratio were CN_734869 (41,059,585 bp) and SNP_A-4247687 (41,570,665 bp), respectively (Fig. 1).

The genomic fragments deleted in our patients overlapped with classical deletion described in literature. The array analysis of the parents showed no abnormalities in both cases. This finding indicated that the deletions were *de novo.*

3.4 MLPA/ FISH analysis

MLPA analysis confirmed the deletion in the proband samples (Fig. 2). In the first patient the FISH analysis confirmed the presence of deletion. FISH did not show deletion of chromosome region 17q21.31 in parents.

4. DISCUSSION:

SNP array screening for intellectual disability associated with mild dysmorphic features in our patients revealed a microdeletion of the 17q21.31 region. Considering the phenotypic characteristics described by Koolen *et al.*, [2] both patients only showed a limited number of features: in particular, facial dysmorphisms became more typical only with increasing age.

Neuroimaging confirmed the already reported developmental anomalies of the corpus callosum, the cyngulate gyrus and the lateral ventricles [2,3]. The main central nervous system defects described in syndrome are: agenesis/dysgenesis of corpus callosum, abnormally shaped hippocampus, ventriculomegaly, periventricular white matter lesions and bilateral subependymal heterotopia. Koolen *et al.* also described a case with communicating hydrocephalus [2]. Recently, neuroimaging studies revealed an abnormality of the pituitary region consisting of a thin pituitary stalk, no visible posterior pituitary hypersignal and anterior pituitary hypoplasia, in a patient with the 17q21.31 microdeletion and partial pituitary stalk interruption syndrome (PSIS) [10].

In the first patient brain MRI did not show any malformations but only a nonspecific temporal horn asymmetry and some Virchow-Robin dilatations. The negative neuroradiological features are associated in this case with an unremarkable neurological exam and a moderate intellectual disability, which remained stable during the neuropsychological follow-up.

Instead, in the second patient MRI showed an Arnold-Chiari malformation type 1 [OMIM ID: 118420], coexisting with a mild brainstem malformation characterized by prominence of the left olive over the surface of the medulla oblongata. This is the first report of an association between CM1 and 17q21.31 microdeletion syndrome. Chiari malformation type 1 is considered a multifactorial condition although familial cases also suggest a genetic component [11]. The likelihood that CM1 can be genetically transmitted has been suggested by two lines of evidence: the association of CM1 with known genetic disorders, such as achondroplasia, Hajdu-Cheney syndrome, Klippel-Feil syndrome or neurofibromatosis type 1 [12]. Furthermore, case reports of familial aggregation, including cases of monozygotic twins and triplets concordant for CM1 are reported in the literature [11,12].

Boyles *et al.* [12] identified with genome linkage analysis some candidate loci associated with CM1 on chromosome 15q21.1-q22.3 and 9q22.31. However, a revision of the literature did not show any association between genes encompassed by the 17q21.31 deletion and CM1.

Notwithstanding CM1, our patient did not show any significant clinical (headache, cranial nerve dysfunction, neck pain and cerebellar involvement with vertigo or ataxia) or neurophysiological (auditory brain stem evoked potentials) signs of brain stem involvement. Neurological examination revealed a mild muscle hypotonia in all four limbs with bilateral hyperactive knee jerks. To rule out the possibility of visual disturbances provoked by CM1, she underwent electrophysiological tests of the visual pathway (visual evoked potentials and electroretinogram) that turned out to be normal. Nevertheless, our case with Chiari malformation type 1 will undergo a neurological, neuroimaging and neurosurgical follow-up in order to avoid complications, due to compression of the neural structures by the herniated tonsils. In the 17q21.31 microdeletion syndrome, the degree of developmental delay varies significantly, but the majority of individuals show an intellectual disability in the mild to moderate range. We did not find any significant differences compared to what has already been reported in the literature. Our patients exhibited a mild-moderate degree of intellectual disability with speech delay: serial assessments of intellectual proficiency have been of importance in order to rule out a worsening of cognitive functions with increasing age. In fact, in contrast with Rademakers *et al*. [13], Rovelet-Lecrux *et al*. identified a heterozygous genomic deletion of the *MAPT* gene, encompassed by the 17q21.31 microdeletion, in a patient with frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) [OMIM ID: 600274] [14]. Whether tau toxicity in FTDP-17 is the consequence of a loss of function mechanism or of an aberrant gain of function resulting from its aggregation remains an open question [15]. To the best of our knowledge, we still lack a report of a long term follow-up of patients with the 17q21.31 syndrome that would allow to detect a possible onset of FTDP-17, between the third and fifth decades. The role of neuroimaging should be stressed even in patients with unrevealing neurological exam and slightly delayed intellectual functioning. An ongoing surveillance of cognitive efficiency in patients with the 17q21.31 microdeletion syndrome could be a valuable tool in the early detection of a possible cognitive decline thus allowing the implementation of effective early intervention strategies. In conclusion, we suggest that Chiari malformation type I should be considered in patients with the 17q21.31 microdeletion syndrome who present persistent headache, neck pain, or other suggestive symptoms.

REFERENCES

[1] Grisart B, Willatt L, Destrée A. 17q21.31 microduplication patients are characterized by behavioural problems and poor social interaction. J. Med. Genet. 2009; 46: 524-530.

[2] Koolen DA, Sharp AJ, Hurst JA. Clinical and molecular delineation of the 17q21.31 microdeletion syndrome. J. Med. Genet. 2008; 45: 710-720.

[3] Dubourg C, Sanlaville D, Doco-Fenzy M. Clinical and molecular characterization of 17q21.31 microdeletion syndrome in 14 French patients with intellectual disability. Eur. J. Med. Genet. 2011; 54: 144-151.

[4] Stefansson H, Helgason A, Thorleifsson G. A common inversion under selection in Europeans. Nat. Genet. 2005; 37: 129–137.

[5] Rao PN, Li W, Vissers LE. Recurrent inversion events at 17q21.31 microdeletion locus are linked to the MAPT H2 haplotype. Cytogenet. Genome Res. 2010; 129: 275–279.

[6] Wechsler D. Wechsler Preschool and Primary Scale of Intelligence (WWPSI). Florence: Organizzazioni Speciali. 1973.

[7] Wechsler D. Wechsler Intelligence Scale for Children–Revised (WISC-R). Florence: Organizzazioni Speciali. 1986.

[8] Kaufman J, Birmaher B, Rao U. Diagnostic interview for evaluation of psycopathological disorders in children and adolescents (K-SADS-PL). Trento: Erickson Editions. 2004.

[9] Sparrow Sara S, Balla David A., Cicchetti Domenic V. Vineland Adaptive Behavior Scales (VABS). Florence: Organizzazioni speciali. 2003.

[10] El Chehadeh-Djebbar S, Callier P, Masurel-Paulet A. 17q21.31 microdeletion in a patient with pituitary stalk interruption syndrome. Eur. J. Med. Genet. 2011; 54: 369-373.

[11] Milhorat H, Chou MW, Trinidad EM. Chiari I malformation redefined: clinical and radiographic findings for 364 symptomatic patients. Neurosurgery 1999; 44: 1005–1017.

[12] Boyles AL, Enterline DS, Hammock PH. Phenotypic definition of Chiari type I malformation coupled with high-density SNP genome screen shows significant evidence for linkage to regions on chromosomes 9 and 15. Am. J. Med. Genet. 2006; 140: 2776-2785.

[13] Rademakers R, Cruts M, van Broeckhoven C. The role of tau (MAPT) in frontotemporal dementia and related tauopathies, Hum. Mutat. 2004; 24: 277–295.

[14] Rovelet-Lecrux A, Lecourtois M, Thomas-Anterion C. Partial deletion of the MAPT gene: a novel mechanism of FTDP-17. Hum. Mutat. 2009; 30: 591-602.

[15] Feinstein SC, Wilson L. Inability of tau to properly regulate neuronal microtubule dynamics: a loss-of-function mechanism by which tau might mediate neuronal cell death. Biochim. Biophys. Acta. 2005; 1739: 268-279.

Fig. 1 Results of Affymetrix SNP 6.0 Array. Copy number state of each probe is drawn along chromosome 17 from 39.000.000 to 43.000.000 bp (NCBI Build 36). The upper panel represents the copy number state of patient 1, the middle panel represents the copy number state of patient 2. Values of Y-axis indicate the inferred copy number according to probe intensities.

Fig. 2 Bar chart that summarizes the results of multiplex-ligation-dependent probe amplification (MLPA) for (A) patient 1 and (B) patient 2.

Patient 1

Fig. 3 a) TSE T2 weighted coronal image: posterior white matter little dilatation of some Virchow-Robin spaces.

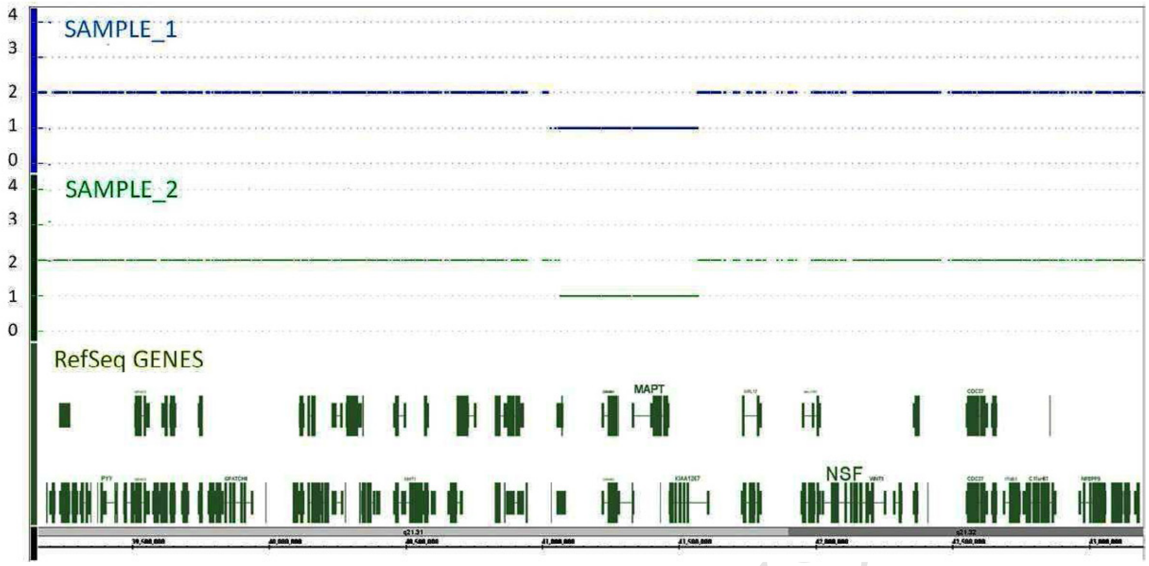
Fig. 3 b) TSE T2 weighted coronal image: left temporal horn dilatation but normal signal of the hippocampus.

Patient 2

Fig. 4 a) TFE T1 3D weighted sagittal image: dismorphism of the corpus callosum, with hypoplasia of the splenium and of the rostrum and thickening of the anterior part of the body and of the genu. Erniation under the occipital foramen of the cerebellar tonsils, for Chiari I malformation.

Fig. 4 b) TFE T1w 3 D weighted coronal MPR reconstruction image: little reduction of the right hippocampus probably correlated with incomplete or anomalous rotation, with associated dilatation of the ipsilateral temporal horn.

Fig. 4 c-d) TFE T1w 3 D weighted axial MPR reconstruction images: dismorphic profile of the medulla oblongata characterized by a protrusion of the left anterolateral portion.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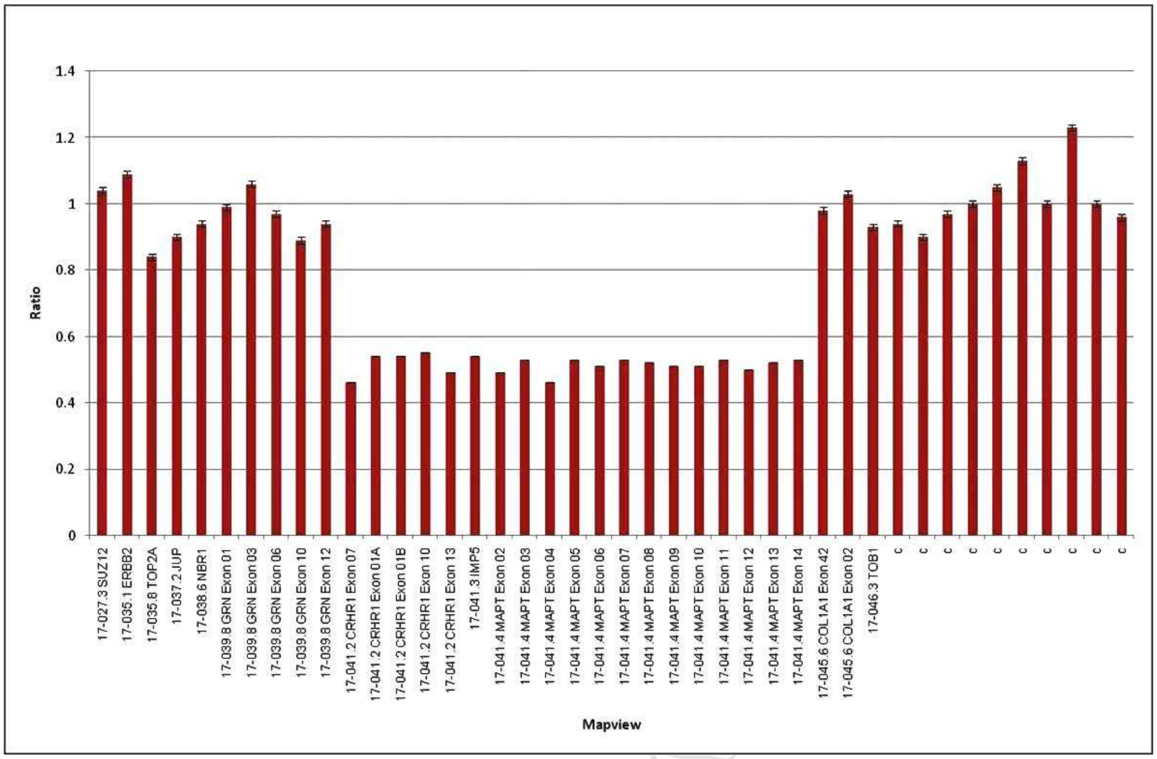
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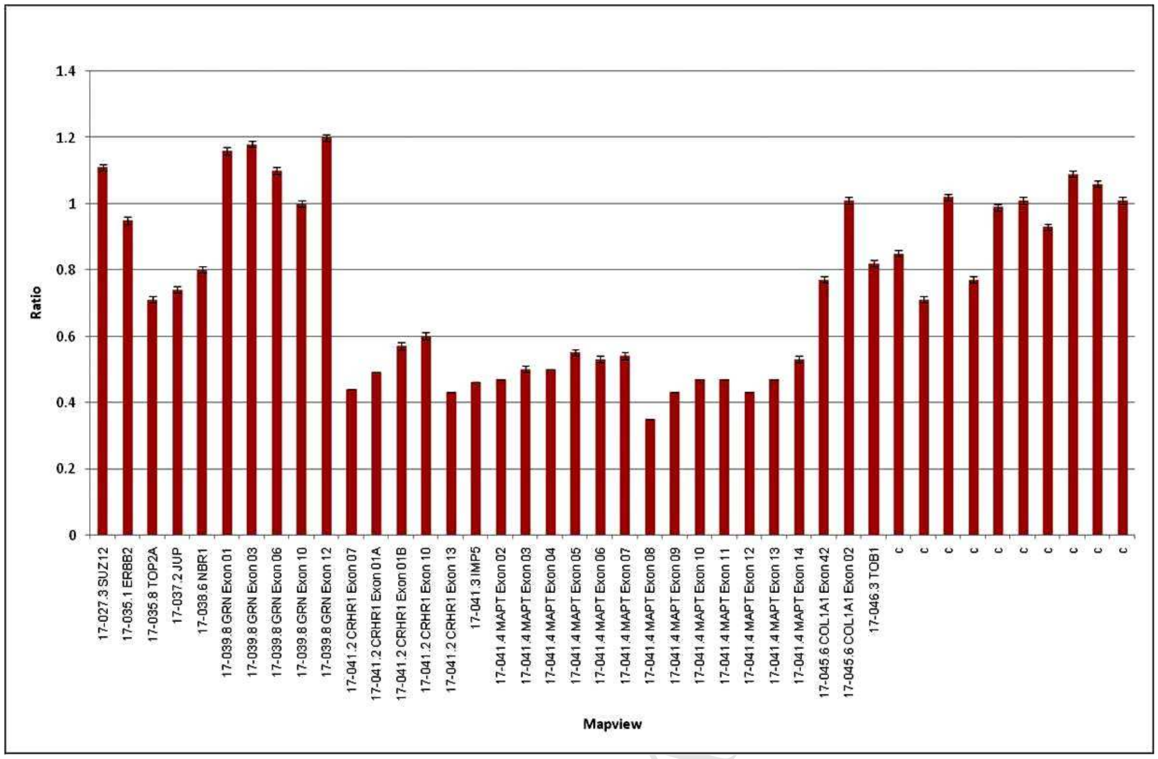
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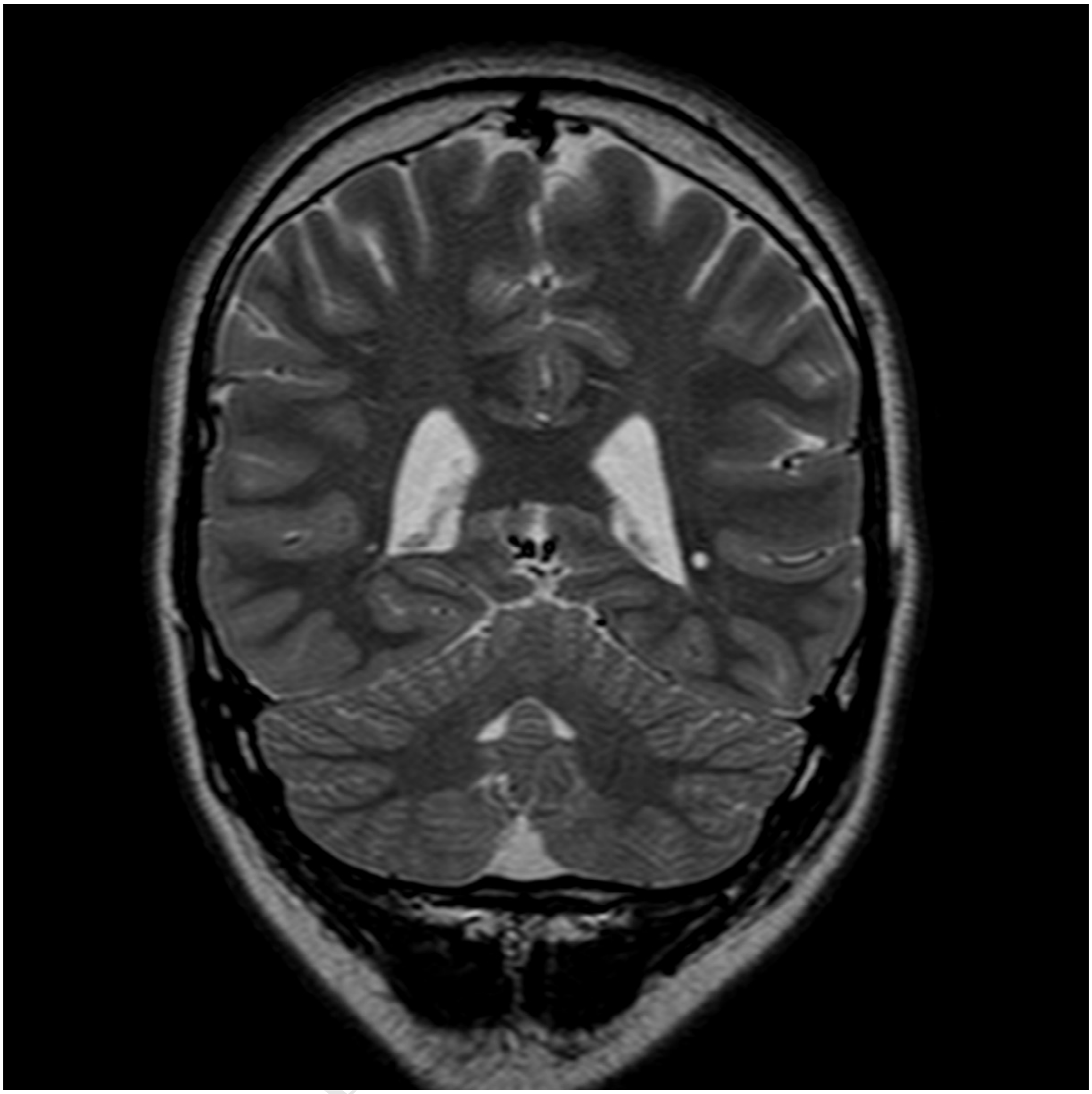

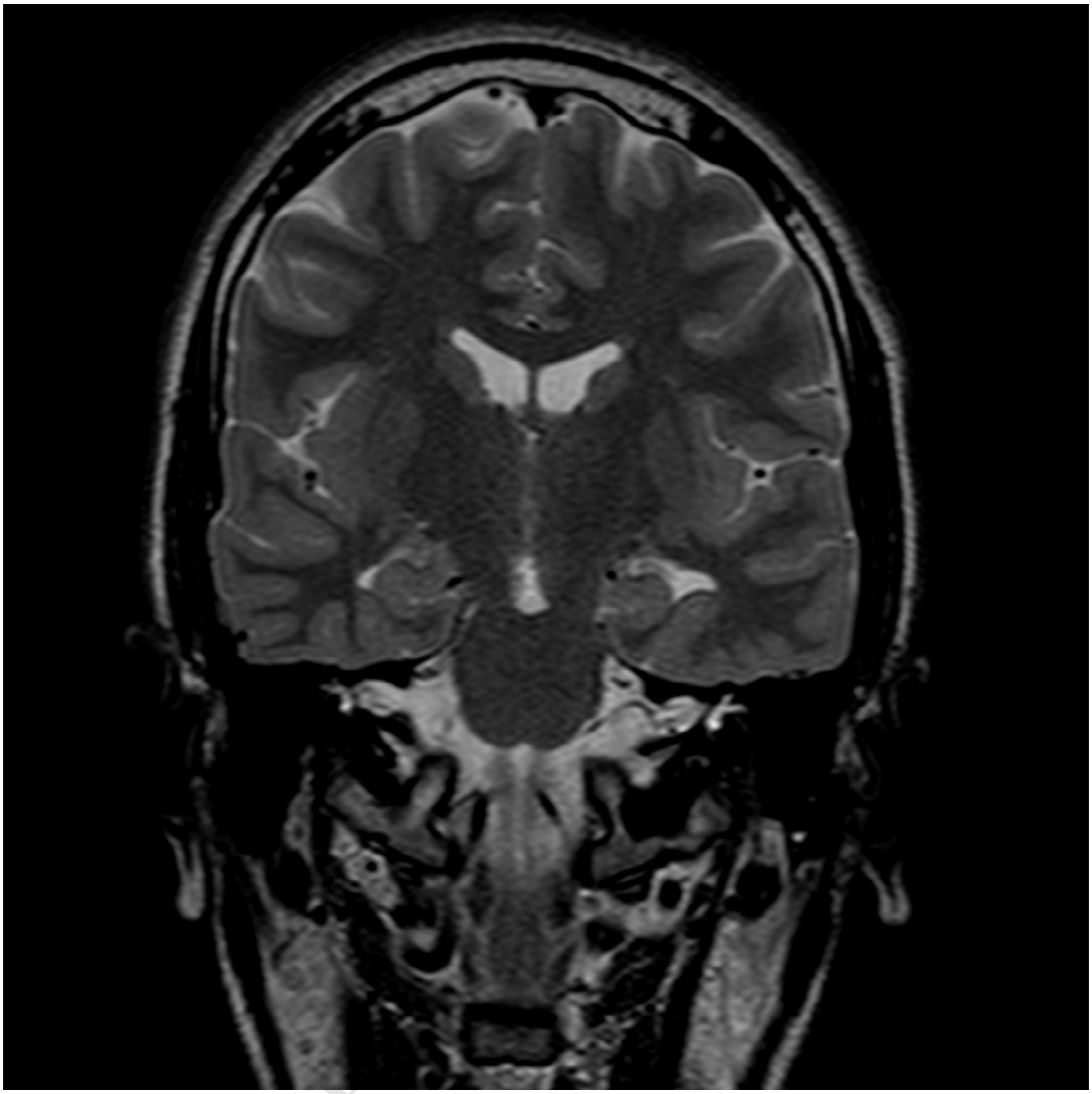

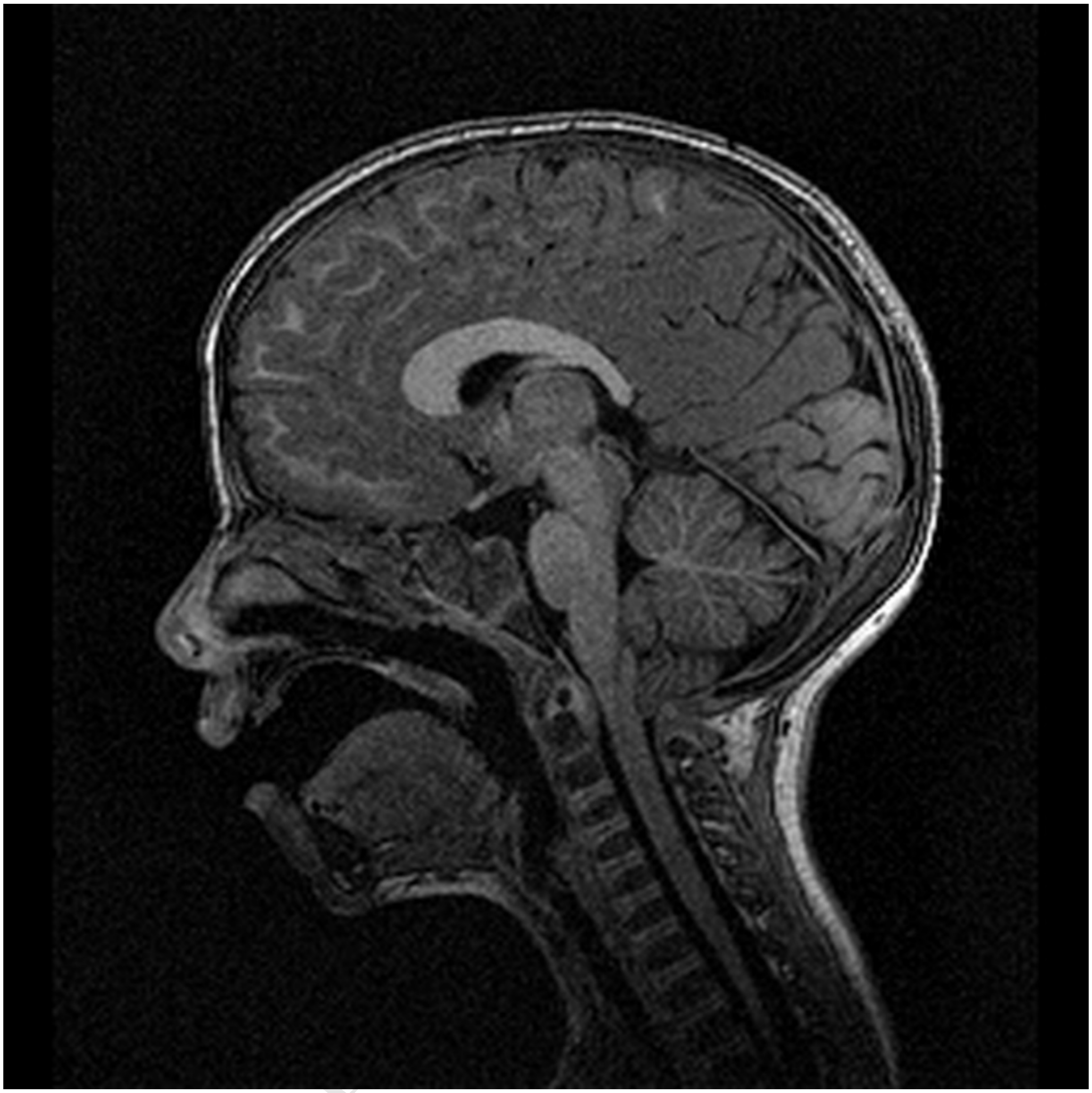

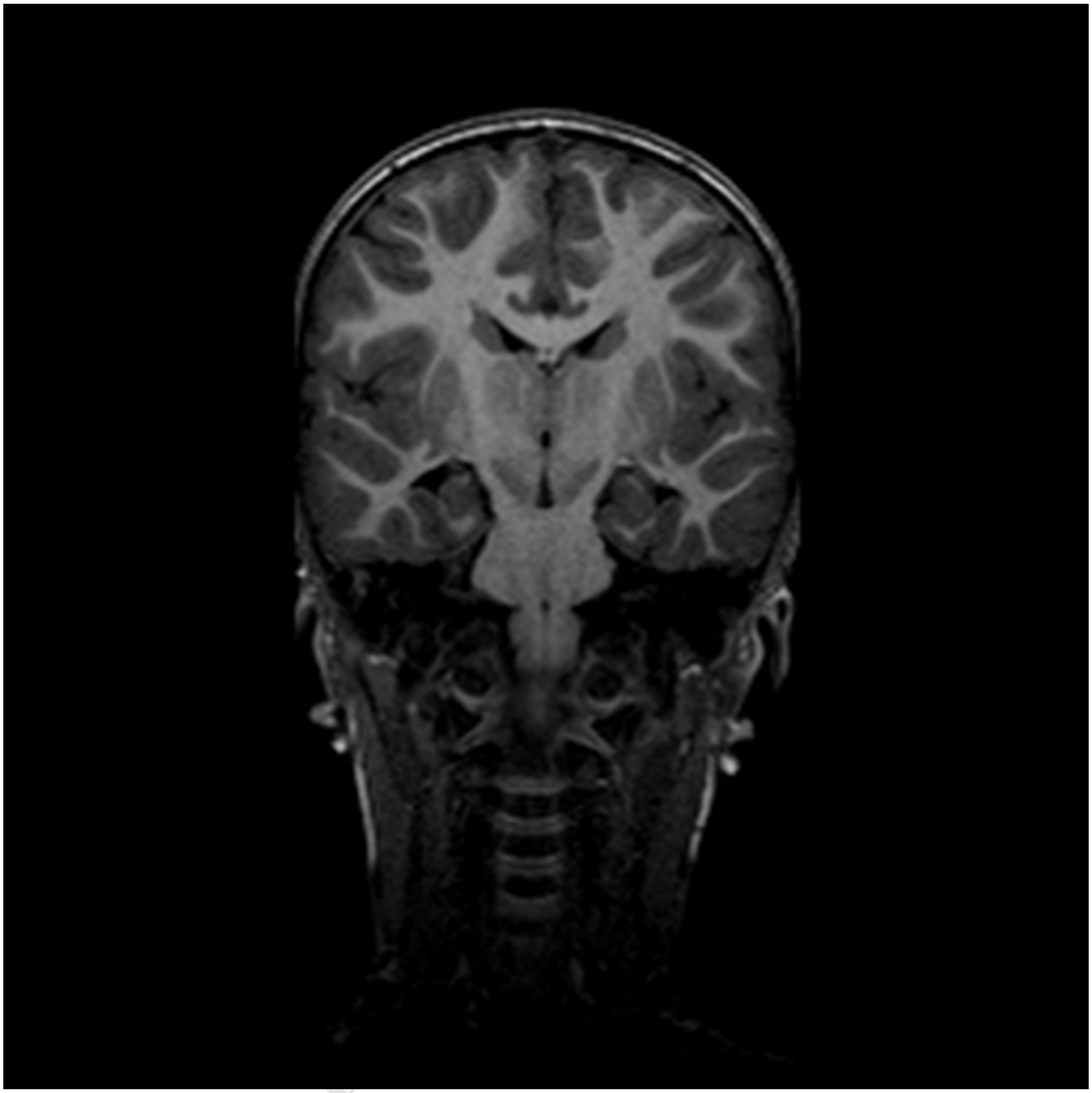

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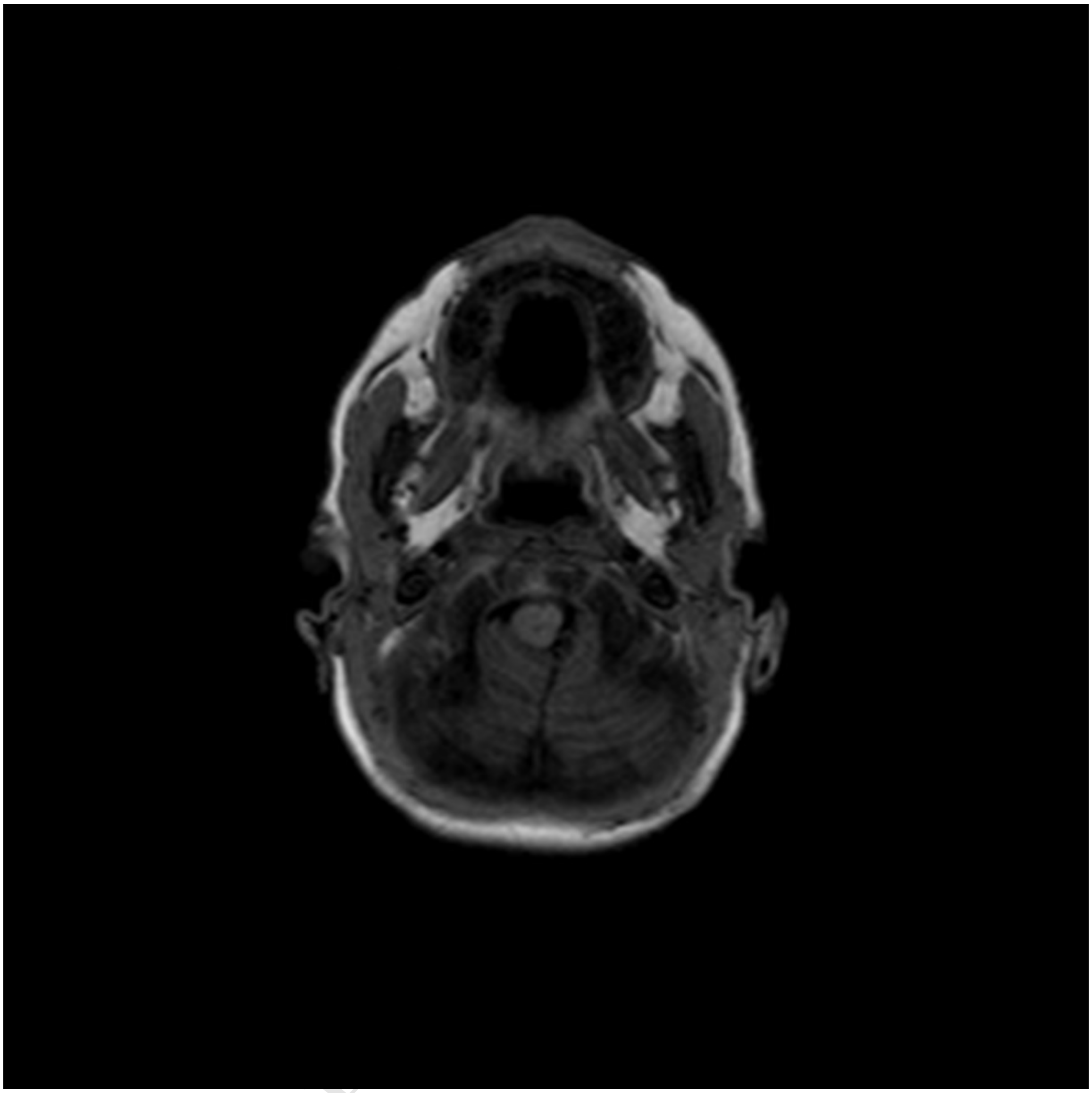

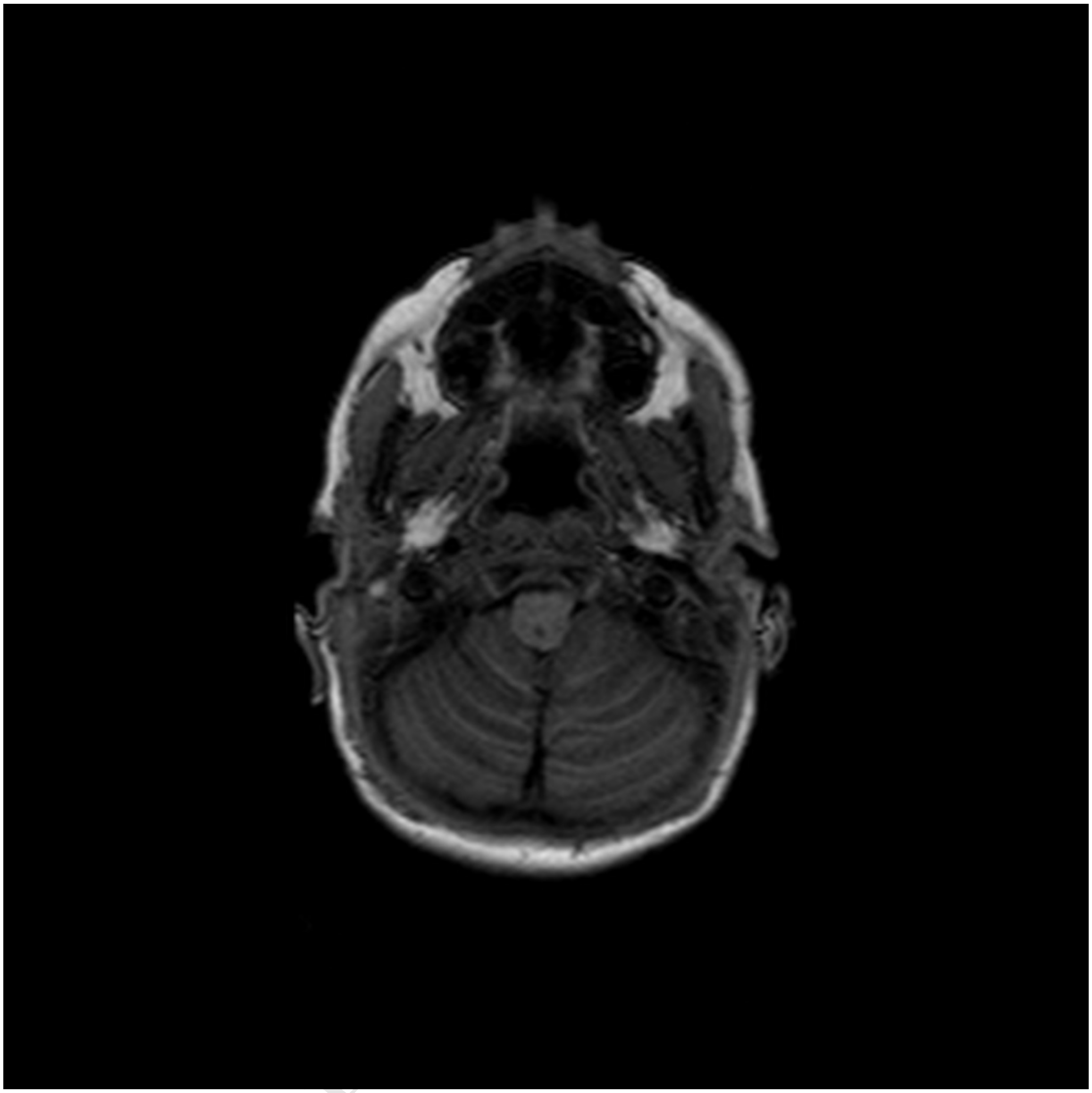ACCEPTED