



HAL
open science

Normal intellectual skills in patients with Rhombencephalosynapsis

Marie-France Bonnetain, Christelle Rougeot-Jung, Catherine Sarret, Laurence Lion-François, Olivier Revol, Emeline Peyric, Juan Velazquez-Dominguez, Anne Miret, Massimiliano Rossi, Mona Massoud, et al.

► **To cite this version:**

Marie-France Bonnetain, Christelle Rougeot-Jung, Catherine Sarret, Laurence Lion-François, Olivier Revol, et al.. Normal intellectual skills in patients with Rhombencephalosynapsis. *European Journal of Paediatric Neurology*, 2020, 29, pp.92-100. 10.1016/j.ejpn.2020.09.007 . hal-03124493

HAL Id: hal-03124493

<https://hal.science/hal-03124493>

Submitted on 16 Dec 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Rhombencephalosynapsis with normal intellectual skills: six new cases and a review of the literature

Normal intellectual skills in patients with Rhombencephalosynapsis.

Marie-France Bonnetain (1), Christelle Rougeot-Jung (2), Catherine Sarret (3), Laurence Lion-François (2), Olivier Revol (4), Emeline Peyric (2), Juan Velazquez-Dominguez (2), Anne Miret (3), Massimiliano Rossi (5, 9), Mona Massoud (6), H el ene Laurichesse - Delmas (7), Laurent Guibaud (8, 9), Vincent des Portes (2, 9).

1 Department of Pediatrics, Hospital of Chambery, University Hospital of Grenoble, France

2 Department of Pediatric neurology, Competence Centre for cerebellar Malformations, Lyon University Hospital, F-69677, Bron, France

3 Department of Pediatric Neurology, CEMC Auvergne, Clermont-Ferrand University Hospital, Clermont-Ferrand, France

4 Department of psychopathology, Lyon University Hospital, F-69677, Bron, France

5 Genetics department, Referral centre for developmental abnormalities, Lyon University Hospital, and INSERM U1028, CNRS UMR5292, Lyon Neuroscience Research Centre, GENDEV Team, Lyon, France

6 Department of obstetrics, Lyon University Hospital, F-69677, Bron, France

7 Department of obstetrics, CEMC Auvergne, Clermont-Ferrand University Hospital, Clermont-Ferrand, France

8 Department of Pediatric Radiology and Fetal Medicine, Lyon University Hospital, F-69677, Bron, France

9 University Lyon 1, F-69008, Lyon, France.

Abstract (276 words)

Objectives: Rhombencephalosynapsis (RES) is a very rare cerebellar malformation. Neurodevelopmental outcome of *apparently* isolated RES remains poorly documented and standardized cognitive assessment, reported in only nine published cases so far, is lacking. Prenatal counselling is challenging considering the uncertain prognosis of isolated RES. The aim of this study was to focus on cognitive and motor outcome of isolated RES with a clinical description of six new cases and a detailed review of the literature.

Methods: A single-centre retrospective study of all RES patients over a 15-year period. Ataxia and fine motor skills were scored using a five-grade scale, according to the degree of disturbance of

daily living. Intelligence Quotient (IQ) was established according to age-related Weschler Intelligence Scales. A systematic literature review included published cases with relevant outcome data.

Results: Six new cases of apparently isolated RES were reported, including three diagnosed in prenatal settings. The onset age for walking was delayed in four patients. Three patients had head shaking and three had a strabismus. One patient had a mild motor disability, one had subtle ataxia that did not impair daily life and four patients had a normal neurological examination at the last visit. Intellectual abilities were normal in all patients (full IQ score from 90 to 142), although three had ADHD. All received standard schooling. Based on these six new cases, as well as cases from 12 publications in the literature, a total of 28 patients with non-syndromic RES were analysed. Concerning motor outcome, 72% had no complaint or minimal impairment, 16% moderate and 12% severe impairment. Concerning cognitive outcome, 68% had normal cognitive skills, 18% borderline intellectual functioning and 14% moderate to severe disability.

Keywords

rhombencephalosynapsis; cognitive outcome; intellectual abilities; attention deficit hyperactivity disorder; prenatal counselling; vermis; magnetic resonance imaging

Abbreviations

ADHD: Attention Deficit Hyperactivity Disorder; DSM: Diagnostic and Statistical Manual of Mental Disorders; GLC: General Language Composite; GLH: Gomez-Lopez-Hernandez (syndrome); IQ: Intelligence Quotient; OFC: Occipital-Frontal Circumference; PIQ: Perceptual Intelligence Quotient, PRI: Perceptual Reasoning Index; PSI: Processing Speed Index; PSQ: Processing Speed Quotient; RES: Rhombencephalosynapsis, TCD: Transverse Cerebellar Diameter; VCI: Verbal Comprehension Index; VIQ: Verbal Intelligence Quotient; WPPSI: Wechsler Preschool and Primary Scale of Intelligence; WISC: Wechsler Intelligence Scale for Children; WMI: Working Memory Index.

Address of correspondence: Vincent des Portes, Centre de compétence « Malformations cérébelleuses », Hôpital Femme Mère Enfant, Hospices Civils de Lyon, F-69677, Bron, France. [vincent.desportes@chu-lyon.fr]; Phone: 33 4 27 85 53 82.

Funding source. No funding. The authors have no financial relationships relevant to this article to disclose.

Potential Conflicts of Interest: The authors have no conflicts of interest relevant to this article to disclose.

Contributors' Statement

MF Bonnetain and V des Portes designed the study, drafted the manuscript, revised the manuscript and approved the final manuscript as submitted.

C Rouget-Jung, C Sarret, L Lion-François, O Revol, M Rossi, contributed to clinical data and carried and approved the final manuscript as submitted.

M Massoud and H Laurichesse contributed to prenatal diagnosis of some cases, revised the manuscript and approved the final manuscript as submitted.

J Velazquez-Dominguez, E Peyric and A Miret performed all psychometric assessments and contributed to data analysis, and approved the final manuscript as submitted.

L Guibaud checked all US and MRI data, included MRI figures, critically reviewed the manuscript, and approved the final manuscript as submitted.

Word Number: 3410 words.

Introduction

Rhombencephalosynapsis (RES) is a rare cerebellar malformation defined by partial or complete agenesis of the vermis and fusion of the cerebellar hemispheres and dentate nuclei [1-5]. RES is frequently associated with other abnormalities (aqueductal stenosis, mesencephalosynapsis, holoprosencephaly, corpus callosum dysgenesis, microlissencephaly, pontocerebellar hypoplasia, extra-cerebral malformations, and chromosomal anomalies) [6-9, 45] or occurs as a syndromic form, such as VACTERL syndrome [8], or the recently described *MNI* or gene-related syndromic RES [9]. The most common syndrome related to RES is Gomez-Lopez-Hernandez syndrome (GLHS) or cerebello-trigeminal-dermal dysplasia, comprising scalp alopecia, inconsistent trigeminal anaesthesia and craniofacial features, short stature and kidney malformation [10-12]. Apart from the very rare syndromal genetic constellation (e.g associated with mutations in *MNI*)

patients with RES and GLH are sporadic observations and the recurrence risk for a couple is extremely low [5].

Classically, patients with RES present with motor developmental delay, ataxia, and the characteristic “figure-of-eight” head shaking [13, 14]. The range of cognitive outcome is very large, from profound intellectual disability to normal IQ. Syndromic forms of RES, such as VACTERL, are associated with severe cognitive prognosis [2], but patients with GLHS may have a good cognitive prognosis if no additional brain malformation exists [2, 11].

If such condition can be diagnosed postnatally, advances in prenatal imaging have resulted in an increasing number of prenatal diagnoses of abnormalities of the posterior fossa, including RES [46]. In foetal medicine practice, RES is diagnosed in *two very different settings*. Indeed, RES can be diagnosed when facing *severe ventriculomegaly* in the early second trimester when RES is associated with other cerebral malformation, involving especially the mesencephalon and diencephalon, as we have previously described [30]. In such setting, most cases lead to termination of pregnancy due to severe obstructive ventriculomegaly of poor postnatal outcome. On the other hand, RES can be prenatally diagnosed on the basis of an *isolated* reduced transverse cerebellar diameter (TCD), detected in the second or last trimester, without severe ventriculomegaly or associated malformation, leading to the diagnosis of *apparently* isolated RES. In such setting the diagnosis can be easily overlooked.

When *apparently* isolated RES is detected, prenatal counselling remains challenging due to confusing/poor literature regarding the post-natal outcome: short follow-up and lack of cognitive assessments with psychometric batteries, which have been reported for only nine published cases [15-19]. In attempt to overcome this issue, we report the radiological, developmental and cognitive features of six individuals with *apparently* isolated RES *at the time of diagnosis*, including three detected in prenatal settings.

Materials and methods

A retrospective study was conducted at the University Hospital of Lyon from 2003 to 2018, which aimed to provide a description of the cognitive outcome of all patients with apparently isolated RES. Children were included through two different settings, based on: (1) *prenatal* detection of a reduced TCD on foetal ultrasound leading to the diagnosis of “apparently isolated” RES on foetal MRI; or (2) *postnatal* diagnosis of isolated RES on brain MRI indicated for developmental delay or abnormal movement of the head.

Inclusion criteria were an unequivocal diagnosis of RES on *postnatal* brain MRI, with fusion of the cerebellar hemispheres across the midline, as judged on axial plane, and transverse folial orientation on posterior coronal MRI sections (Fig. 1).

Exclusion criteria were additional anomalies at diagnosis (cerebral or extra-cerebral malformation) and chromosomal anomalies. More specifically, fetuses with severe ventriculomegaly (15 mm or more) and/or aqueductal stenosis were excluded. Minor (10-11mm) or moderate (12-14 mm) foetal ventriculomegaly was not considered an exclusion criterion.

Clinical data were collected from the clinical records: age at diagnosis, sex, ante-perinatal features, clinical signs at diagnosis, clinical examination, treatment, cognitive assessment, schooling and brain MRI.

Ataxia, dysmetria and fine motor skills were scored using a five-grade scale, according to the degree of disturbance of activities of daily living, adapted from Poretti *et al.* [20]: (1) *severe*: unable to walk unassisted; (2) *moderate*: wide-based gait, frequent falls, and overt dysmetria; (3) *mild*: infrequent falls, gross motor problems, and fine motor difficulties in drawing or writing; (4) *minimal*: very mild gait ataxia or dysmetria on neurological examination without consequences on daily-life activities; and (5) no complaint and normal neurological examination.

Intelligence Quotient (IQ) was established according to Wechsler Intelligence Scales: the Wechsler Pre-school and Primary Scale of Intelligence 3rd edition (WPPPSI-3) [21], the Wechsler Intelligence Scale for Children 4th edition (WISC-4) [22] and the Wechsler Intelligence Scale for Adults 4th edition (WAIS-4) [23]. Attention deficit hyperactivity disorder (ADHD) was diagnosed

according to the DSM-IV criteria and KiTAP computerized battery [24]). For Patient 5, the Psychomotor Development Index was obtained alongside the French Brunet Lézine Development Scale [25].

Ethical issues. The clinical follow-up was performed within the frame of routine clinical visits and no further written consent was required from parents. Neither photographs nor blood samples were specifically required for the study.

Results

Twenty-three cases of RES were diagnosed during the inclusion period (figure 2, see also Table 5 suppl. data). Among the 12 pregnancies, 8 had obstructive VM. Only 4 fetuses had an apparently isolated RES, leading to one termination of pregnancy and three births. Among the 11 children diagnosed with RES after birth, 7 had a syndromic RES with other malformation and/or chromosomal anomaly. Only 4 had isolated RES. One case has already been published [19] and this patient was therefore excluded from the series.

Finally, this series included six patients with *apparently* isolated RES at the time of diagnosis. Three were diagnosed in prenatal settings driven by a small Transverse Cerebellar Diameter (TCD) on foetal ultrasound without obstructive ventriculomegaly or obvious associated malformation. Three were referred postnatally based on clinical signs. Detailed clinical histories of the six cases are provided as supplementary material (see online supplementary data). Relevant clinical, cognitive and MRI findings are summarized in Tables 1-3 and Fig. 1, 2.

Clinical features (Table 1). Among the three cases diagnosed postnatally, brain MRI was requested due to a delay in walking (Patient 2) and mild ataxia (Patients 3 and 6). The onset age for walking (from 17 to 36 months) was delayed in four patients. According to the ataxia/fine motor skills scale, Patient 1 had a *mild disability* due to motor and visuospatial dyspraxia with impaired writing (Table 2 and supplementary data); Patient 4 had minimal impairment with a transient delay in fine motor and graphic skills and subtle ataxia that did not impair walking in daily life; and Patients 2, 3, 5 and

6 had slightly delayed walking or transient ataxia that improved, with a normal neurological examination at the last visit. Three patients had stereotyped side-to-side head shaking and three had a strabismus. Two patients had growth hormone (GH) deficiency, including Patient 1 who fulfilled Gomez-Lopez-Hernandez (GLH) syndrome criteria.

Imaging data. All patients had postnatal brain MRI (Fig. 1). In all cases, the hemispheres were fused on the midline on coronal images, tangential to the most posterior part of the cerebellum (Fig. 1; C1-C6). On mid-sagittal images, neither the primary fissure nor the pre-pyramidal fissure was identified on the cerebellum (Fig. 1; A1-A6). One should note that although fusion of the two dentate nuclei is a cardinal feature of RES based on pathological specimens, this feature can only be clearly identified on MRI in neonates because of the hyperintensity of these two nuclei on T2-weighted imaging (Fig. 1; B3, B5 [small arrows]) which disappears later in life.

We considered RES as *complete* (Patient 1, 4, and 6) if the inferior borders of the cerebellar hemisphere at the level of cerebellar tonsils were fused on the midline (Fig. 1; D1, D4, D6 [asterisk]) without identification of any incisure between the two cerebellar tonsils (Fig. 1; D1, D4, D6 [large arrow]), and RES as *partial* (Patient 2, 3, 5) when an incisure between two cerebellar tonsils was present (Fig. 1; D2, D3, D5), with identification of a small nodulus between them in some cases (Fig. 1; D2 [thin white arrow]).

Other visible abnormalities were spinal cord lipoma (Patient 1; data not shown) and ventriculomegaly (patient 4 who required a ventriculoperitoneal shunt and patient 2 with mild VM). Despite a normal length of the corpus callosum (10e p), a short splenium and rostrum was noteworthy in Patient 5. No other associated brain malformation, such as thalami fusion or grey matter heterotopia, was revealed on postnatal MRI.

Cognitive assessments: Five patients had an IQ assessment between 5 and 21 years old (WPPSI-III or WISC-IV or WAIS-IV). The cognitive profiles, detailed in Table 2 and Fig. 3, were quite homogeneous. IQ score was normal for four patients and high for one patient. The Working Memory and Processing Speed were weaker in patient 1 who had dyspraxia and ADHD. Other

patients who had a deficit in fine motor skills improved with age. Interestingly, for Patient 5 who had a delay in walking, the developmental index improved from 12 to 24 months old with normal developmental skills in all domains and very good language abilities (Table 3). Three of five patients had ADHD based on DSM IV criteria. For two of them, the KiTAP computerized battery, performed at the age of five years and 11 years, respectively, showed sustained attention deficit, sensitivity to a distractor, mental flexibility deficit, motor inhibition deficit and impulsiveness. Divided attention appeared to be spared (Table 2). Attention deficit was significantly improved on methylphenidate in both treated patients.

Discussion

In this study, we considered “apparently isolated RES” as RES without additional brain malformation, severe ventriculomegaly or chromosomal anomalies *at diagnosis*, especially when detected in prenatal settings. However, it has been reported that such a continuous series of associated congenital anomalies precludes RES from being clearly separated into distinct “syndromic” and “isolated” entities [5]. Indeed, for Patient 1 of this series who was considered to have “apparently isolated RES” in prenatal settings, other malformations (heart, kidney, spina lipome, craniofacial dysmorphism) leading to GLHS were revealed only after birth. This pitfall of GLHS diagnosis in prenatal settings has been previously mentioned, since neuroimaging does not allow to distinguish between isolated RES and GLHS [10]. In previous series of patients with GLH, developmental outcome was variable, from severe cognitive disability to normal cognitive skills [2, 10]. Despite good intellectual abilities, additional motor and/or genital, urinary, and bowel dysfunction, which may occur in GLHS, should lead to careful investigation of extracerebral malformations, including spinal cord defect, on prenatal ultrasound. As far as we know, spinal cord defect has not been previously described in GLHS. Nevertheless, bladder dysfunction was reported in one patient [10] and tethered cord or lumbosacral myelomeningocele has been previously described with RES [5, 26-28].

In search of prognostic factors, which should be useful in prenatal settings for couples facing an apparently isolated RES, we carefully analysed published case reports with reliable data on cognitive and motor outcome (Table 4). We excluded from this review published cases of RES associated with obvious major malformations contributing to a severe condition (holoprosencephaly, diffuse pachygyria, obstructive hydrocephaly due to pathologies of differentiation of the diencephalon or mesencephalon, multiple congenital anomalies, syndromic RES such as VACTERL, chromosomal defects, *etc.*). We did not include data from the largest series of 42 RES cases by Ishak *et al.* [2], despite the fact that this was overall very informative, for three reasons: (1) detailed developmental and neurological data on *individual* cases were not available; (2) outcome categories did not separate cognitive and motor skills; and (3) according to the authors, the cohort was likely skewed towards more severely affected subjects with associated abnormalities due to recruitment bias. Also, we did not include GLHS patients since a comprehensive review has already been published [10]. Finally, in addition to the six cases of this series, we reviewed 22 previously reported cases from 12 different publications, and classified the 28 patients into three groups (Table 4): (1) *associated RES* with subtle brain anomalies (such as a thin corpus callosum, fused fornices, heterotopia or focal cortical dysplasia, hippocampal dysplasia) (including our Patient 5); (2) *RES with foetal/congenital hydrocephalus*, that required a shunt (including our Patient 4); and (3) *apparently isolated RES* without associated brain anomalies, extracerebral malformations at diagnosis and/or shunted hydrocephalus after birth (including our Patients 1, 2, 3 and 6).

Concerning *cognitive* outcome, psychometric data were available in 15 patients [15-17, 19, 20] including the six patients of the present series. For the 13 other patients, cognitive outcome was classified according to three grades; “normal”, “mild” and “severe” disability, based on available clinical data. Nineteen individuals (68%) had normal IQ or cognitive outcome, five (18%) had borderline functioning or mild intellectual disability and four (14%) had moderate to profound disability. Among the nine cases with *apparently isolated RES*, seven had normal cognitive skills and one had borderline IQ. The other patient described with a severe outcome was young (18

months) and no clinical or imaging data was available. Among the 13 cases with *subtle brain anomalies*, nine had normal cognitive skills, three had borderline functioning or mild intellectual disability and one had moderate disability. In the third group including six patients with *shunted hydrocephalus*, three had normal cognitive outcome and three had mild to profound intellectual disability.

Concerning *motor* outcome, we scored the 28 cases using a five-grade scale adapted from Poretti *et al.* [20], focusing on the degree of *disturbance in daily life* (Table 4). Among the 28 patients, functional data were not available for three patients with abnormal movements (tics), spastic paraplegia and seizures. Among the 25 other cases, eight (32%) had *minimal* impairment (very mild gait ataxia or dysmetria without consequences on daily-life activities) or no complaint at all, of whom four were classified as isolated RES; 10 (40%) had *mild* impairment (infrequent falls, gross motor problems, and fine motor difficulties in drawing or writing), who were equally divided between isolated RES and those with subtle brain anomalies; and four (16%) had *moderate* (wide-based gait, frequent falls) and three (12%) *severe* (unable to walk unassisted) motor impairment, two of whom had shunted hydrocephalus. These data should, however, be considered with care, as the developmental trajectory of patients was not specified in most reported cases. Knowing that, in our series, four children who had delayed walking and ataxia improved with age, the motor impact of RES might be overestimated, especially for young children.

These data highlight important questions addressing the crucial issue of prognostic factors associated with RES: for example, to what extent might subtle associated brain anomalies and shunted hydrocephalus influence the cognitive outcome of patients with RES? Regarding associated brain anomalies, the association between RES and aqueductal stenosis has already been underlined [29], and a close examination of the third ventricle, thalami, aqueduct of Sylvius and cerebellum is required in order to identify underlying pathologies of differentiation of the diencephalon, mesencephalon, and sometimes telencephalon, leading to severe outcome [2, 20, 30]. Indeed, in the large series of 42 patients [2], a variable degree of mesencephalosynapsis was reported in 52% of

subjects, that ranged from isolated fusion of inferior or superior colliculi, to a mass-like fusion of the entire mesencephalon, extending from the superior cerebellar peduncles up to the level of the posterior commissure. Thirty percent of their subjects also had a lack of olfactory bulbs, suggesting associated forebrain defects.

One of the most frequent associated malformations is corpus callosum dysgenesis, found in more than a third of non-isolated RES [8]. Among the cases gathered in Table 4, it is difficult to determine the mechanism that might be responsible for a “thin corpus callosum”, which may be due to being stretched by an enlarged third ventricle [30] or due to primitive corpus callosum dysgenesis or an insult. Associated thin white matter [31] might be a better clue for a reduced and pathological axonal network. A large majority (eight out of nine) of cases described with a thin or hypoplastic corpus callosum were associated with enlarged ventricles or hydrocephalus (Table 4). Our Patient 5, with a short rostrum and splenium of corpus callosum and normal ventricles, is an exception. Accordingly, in the large series of 42 patients with RES [2], most anterior commissure abnormalities (14/16) were secondary to obstructive hydrocephalus, rather than due to abnormal brain development. Nevertheless, regardless of the mechanism responsible for thin corpus callosum associated with RES, only five of nine patients had good cognitive outcome compared to eight of nine patients with normal ventricle size and corpus callosum (Table 4). The cognitive impact of fused quadrigeminal plates [32] or fused fornices [16, 20] is still questionable, since cognitive outcome of the three published cases varied from mild intellectual disability to normal IQ. In the series of Ishak *et al.* [2], 8/13 patients with fused fornices (62%) had “mild disability” vs 12/14 patients (86%) with normal fornices.

Ishak *et al.* (2) proposed an anatomical classification, dividing RES into four types according to both the presence of nodulus and partial presence of anterior/posterior vermis, and suggested that the degree of clinical severity might be correlated with the degree of cerebellar fusion. However, associated forebrain (16/42) or midbrain malformations or aqueductal stenosis (22/42) with major hydrocephalus were also described in most patients of this series, which might

have influenced the outcome. Moreover, in prenatal settings, the visualization of the precise degree of agenesis of the vermis on foetal MRI might be challenging for radiologists, in particular, to identify the vermian fissure and lobulation [33]. Thus, in our study, we classified patients into only two subtypes: *complete* RES (Patient 1, 4, 6) (Fig. 1; D1, D4, D6), and *partial* RES (Patient 2, 3, 5) based on the presence of an incisure between two cerebellar tonsils (Fig. 1; D2, D3, D5). Since all had good cognitive skills, we did not identify any difference in cognitive outcome related to the subtype of RES (partial or complete) in this small series.

In our series, four patients had strabismus and three had head nodding. In the series of Poretti *et al.* [20], one patient had horizontal nystagmus, one had convergent alternating strabismus and four out of five patients exhibited rhythmical, regular, intermittent head stereotypies corresponding to lateral head nodding. In all cases, these improved in frequency and intensity over the course of several years, but never disappeared. Strabismus and frequent head stereotypies may contribute to impaired social interaction with peers [20] and might require psychological support.

Despite a normal IQ, three patients of our series presented with ADHD. Attention deficit and/or hyperactivity has previously been described in four out of five cases by Poretti *et al.* [20], and in cases with other cerebellar malformations [18, 34, 35]. Moreover, the volume of posterior and inferior vermis is smaller in patients with ADHD and correlates with the intensity of the disorder [36, 37].

Previous authors have hypothesized that the vermis could modulate attentional processes through the fronto-striato-cerebellar tract which connects the prefrontal cortex, the thalamic nuclei, the pons and the cerebellum [38-40]. In a previous study, we described a particular attentional profile in a patient with isolated RES [19]. Reactivity to a visual signal, which appeared at the same time as a distractor, was normal but the patient made more mistakes, possibly due to impulsive reactions and a deficit in motor inhibition. Distraction before the apparition of the target did not disturb the patient, however, the ability to detect the visual distractor, which appeared after the target, was reduced [19]. These data are comparable to the attentional profile of three of our patients

(Table 1). Attentional flexibility, motor inhibition and sustained attention were impaired and selective and divided attentions were preserved.

The vermis might participate in modulating the excitability of the cerebral area, which commands the preparation and control of motor response and attentional flexibility processes. In RES patients, the ability to recognize a pertinent target is preserved. These data tend to support the hypothesis that the vermis has an inhibitory function on cerebral motor areas. Our understanding of the processes involved in attention disorders may enable targeted and early cognitive rehabilitation of patients.

Conclusion

These six new cases of RES with good cognitive outcome reinforce the previously recognized observation that most RES patients without obvious associated malformation and/or obstructive hydrocephaly and/or chromosomal anomaly seem to have preserved intellectual abilities, which is a crucial point for couples' decision following prenatal diagnosis. Nevertheless, ADHD is observed in half of the cases. These data also highlight the involvement of the vermis in attentional processes. Further follow-up of the rare patients born after a prenatal diagnosis of RES is mandatory, in order to more accurately evaluate the rate of preserved intellectual development and associated motor and attention deficit.

Legends of Tables and Figures

Fig. 1. MR images of Patient 1 to 6 performed at nine years, 19 months, 2.5 years, 15 days, seven days and four years, respectively. **A1-A6:** Mid-sagittal T1- (A1, A2, A6) or T2 -(A3, A4, A5) weighted MR images demonstrating, in all cases, an absence of both primary and pre-pyramidal fissures. Note the short splenium and rostrum of the corpus callosum in Patient 5 (A5). **B1-B6:** Axial T2-weighted (B1, B2, B6) or FLAIR (B3, B4, B5) MR images showing fusion of cerebellar hemispheres without identification of any vermian structure. Note that fusion of the two dentate nuclei is clearly identified only in Patient 4 and 5, due to the hyperintensity of the nuclei in

neonates. The dentate nuclei are not identified in the other patients since MRI was performed later in life (between 18 months and nine years). **C1-C6:** Coronal T2-weighted MR images tangential to the most posterior part of the cerebellum showing, in all cases, fusion of the hemispheres on the middle line. On such coronal images, note the characteristic transverse cerebellar folia that straddle the midline with unique transverse folding of the cerebellum (*). **D1-D6:** On more anterior T2-weighted coronal images, absence or presence of incisure (large vertical white arrow) between the medial and inferior borders of the cerebellar hemisphere is identified by the presence (*) or absence of fusion between the two cerebellar tonsils, respectively, allowing, in terms of imaging, to differentiate between complete (Patients 1, 4, 6) and partial RES (Patients 2, 3, 5).

Fig. 2. Flow chart of patients with a diagnosis of RES during the inclusion period.

Fig. 3. Intellectual Quotient scores of Patients 1 to 4 and 6.

BD: Block Design, CD: Coding, CO: Comprehension, DS: Digit Span, FSIQ: Full Scale Intellectual Quotient, GLC: General Language Composite, IN: Information, LNS: Letter Number Sequencing, MR: Matrix Reasoning, PIQ: Perceptual Intellectual Quotient, PC: Picture Concept, PRI: Perceptual Reasoning Index, PC: picture concept, PSI: Processing Speed Index, PSQ: Processing Speed Quotient, SI: Similarities, SS: Symbol Search, VCI: Verbal Comprehension Index, VIQ: Verbal Intellectual Quotient, VO: Vocabulary, WPPSI-III: Wechsler Preschool And Primary Scale of Intelligence Version III, WISC-IV: Wechsler Intelligence Scale for Children Version IV, WAIS-IV: Wechsler Adults Intelligence Scale, Version IV, WR: Word Reasoning, WMI: Working Memory Index.

Table 1. Clinical and radiological features of the six patients.

Table 2. Cognitive features of the five older patients.

(1) VCI: Verbal Comprehension Index or Verbal Index (WPPSI-III); (2) PRI: Perceptual Reasoning Index or Performance Index (WPPSI-III); (3) WMI: Working Memory Index (4) PSI: Processing Speed Index or Processing Speed quotient (WPPSI-III), (5) special needs with teaching assistant.

Table 3. Developmental Index (Brunet-Lezine Scale) for Patient 5, at 12 and 24 months old.

Table 4. Published case reports with reliable data on cognitive and motor outcome.

(n): degree of disturbance scale, adapted from Poretti *et al.* (27). Nyst: nystagmus; strab: strabismus.

* Toelle *et al.* [26]: three patients of this series were not reported in this table; Patient 1, who had further cognitive assessment published by Poretti *et al.* (27); Patient 4, who had confounding factors (foetal valproate exposure and hypoxic ischemic encephalopathy); and Patient 5 who was lost to follow-up.

** Truwit *et al.* [41]: two patients were not included in this table; Patient 2, who had microcephaly and 2q deletion; and Patient 3 who had a fusion of the thalami (diencephalosynapsis).

*** Hydrocephalus was considered when shunt surgery was required. Otherwise, ventriculomegaly was mentioned.

Acknowledgments

The authors thank Oliver Gubbay for language editing. We would especially like to thank the patients and families for their involvement in the clinical follow-up.

References

1. Garel C, Fallet-Bianco C, Guibaud L. The fetal cerebellum: development and common malformations. *J. Child. Neurol* 26 (12) (2011) 148392.
2. Ishak GE, Dempsey JC, Shaw DWW, Tully H, Adam MP, Sanchez-Lara PA, *et al.* Rhombencephalosynapsis: a hindbrain malformation associated with incomplete separation of midbrain and forebrain, hydrocephalus and a broad spectrum of severity. *Brain* 135 (5) (2012) 137086.
3. Poretti A, Boltshauser E. Fetal Diagnosis of Rhombencephalosynapsis. *Neuropediatrics* 46 (6) (2015) 3578.
4. Guibaud L, Lacalm A, Rault E. Fetal ventriculomegaly: diagnostic, ethical and semantic considerations. *Childs. Nerv. Syst* 33 (11) (2017) 18634.
5. Aldinger K, Dempsey J, Tully H, Grout ME, Mehaffey M, Dobyns W, Doherty D. Rhombencephalosynapsis: Fused cerebellum, confused geneticists. *Am. J. Med. Genet. C. Semin. Med. Genet* 178 (4) (2018) 432–439.

6. Sener RN. Unusual MRI findings in rhombencephalosynapsis. *Comput. Med. Imaging. Graph* 24 (4) (2000) 27782.
7. Pavone P, Incorpora G, Ruggieri M. A complex brain malformation syndrome with rhombencephalosynapsis, preaxial hexadactyly plus facial and skull anomalies. *Neuropediatrics* 36 (4) (2005) 27983.
8. Pasquier L, Marcorelles P, Loget P, Pelluard F, Carles D, Perez M-J, *et al.* Rhombencephalosynapsis and related anomalies: a neuropathological study of 40 fetal cases. *Acta Neuropathol.* 117 (2) (2009) 185200.
9. Mak CCY, Doherty D, Lin AE *et al.*: MN1 C-terminal truncation syndrome is a novel neurodevelopmental and craniofacial disorder with partial rhombencephalosynapsis. *Brain.* 143 (1) (2020) 55-68.
10. Poretti A, Bartholdi D, Gobara S, Alber FD, Boltshauser E. Gomez-Lopez-Hernandez syndrome: an easily missed diagnosis. *Eur. J. Med. Genet* 51 (3) (2008) 197-208.
11. Sukhudyay B, Jaladyan V, Melikyan G, Schlump JU, Boltshauser E, Poretti A. Gómez-López-Hernández syndrome: reappraisal of the diagnostic criteria. *Eur. J. Pediatr* 169 (12) (2010) 15238.
12. Rush ET, Adam MP, Clark RD, Curry C, Hartmann JE, Dobyns WB, Olney AH. Four new patients with Gomez-Lopez-Hernandez syndrome and proposed diagnostic criteria. *Am. J. Med. Genet. A* 161A (2) (2013) 320-6.
13. Tully HM, Dempsey JC, Ishak GE, Adam MP, Mink JW, Dobyns WB, *et al.* Persistent figure-eight and side-to-side head shaking is a marker for rhombencephalosynapsis. *Mov Disord* 28 (14) (2013) 201923.
14. Accogli A, Srouf M. Teaching Video NeuroImages: Figure 8 head-shaking stereotypy in rhombencephalosynapsis. *Neurology* 90 (20) (2018) e1832–e1833.
15. Verri A, Uggetti C, Vallero E, Ceroni M, Federico A. Oral self-mutilation in a patient with rhombencephalosynapsis. *J Intellect Disabil Res* 44 (1) (2000) 86-90.
16. Montull C1, Mercader JM, Peri J, Martínez Ferri M, Bonaventura I. Neuroradiological and clinical findings in rhombencephalosynapsis. *Neuroradiology* 42(4) (2000) 272-4.
17. Bell BD, Stanko HA, Levine RL. Normal IQ in a 55-year-old with newly diagnosed rhombencephalosynapsis. *Arch Clin Neuropsychol* 20 (5) (2005) 613-21.
18. Prakash R, Singh LK, Kour J, Mishra B, Lakra A. Psychiatric comorbidities in Dandy-Walker variant disorder. *J Neuropsychiatry Clin Neurosci* 21 (4) (2009) 4779.
19. Michael GA, Garcia S, Bussy G, Lion-François L, Guibaud L. Reactivity to visual signals and the cerebellar vermis: Evidence from a rare case with rhombencephalosynapsis. *Behav Neurosci* 123 (1) (2009) 8696.
20. Poretti A, Alber FD, Bürki S, Toelle SP, Boltshauser E. Cognitive outcome in children with rhombencephalosynapsis. *Eur J Paediatr Neurol* 13 (1) (2009) 2833.
21. Wechsler D. WPPSI III Echelle d'intelligence de WECHSLER pour la période préscolaire et

primaire – 3rd edition. Paris: ECPA (2004).

22. Wechsler D. WISC IV. Echelle d'intelligence de WECHSLER pour enfants et adolescents – 4th edition. Paris: ECPA (2005).

23. Wechsler D. WAIS IV. Echelle d'intelligence de WECHSLER pour adultes – 4th edition. Paris: ECPA (2011).

24. Zimmermann P. Testbatterie zur Aufmerksamkeitsprüfung für Kinder (KITAP). Freiburg: Psytest. 2004.

25. Josse, D. Manuel du Brunet - Lézine Révisé. Echelle de développement psychomoteur de la première enfance. EAP (Editions et Applications psychologiques), Paris, 2001.

26. Toelle SP, Yalcinkaya C, Kocer N, Deonna T, Overweg-Plandsoen WCG, Bast T, *et al.* Rhombencephalosynapsis: clinical findings and neuroimaging in 9 children. *Neuropediatrics* 33 (4) (2002) 209-14.

27. Sener RN, Dzelzite S. Rhombencephalosynapsis and a Chiari II malformation. *J Comput assist Tomogr* 27 (2) (2003) 257-9.

28. Weaver J, Manjila S, Bahuleyan B, Bangert BA, Cohen AR. Rhombencephalosynapsis: embryopathology and management strategies of associated neurosurgical conditions with a review of the literature. *J Neurosurg Pediatr* 11 (3) (2013) 320-6.

29. Barkovich AJ, Raybaud CA. Rhombencephalosynapsis. In *Pediatric Neuroimaging* (5th ed), Barkovich AJ, Raybaud CA (eds). Lippincott Williams & Wilkins: Philadelphia, PA (2012) 473–476.

30. Cagneaux M, Vasiljevic A, Massoud M, Allias F, Massardier J, Gaucherand P, *et al.* Severe second-trimester obstructive ventriculomegaly related to disorders of diencephalic, mesencephalic and rhombencephalic differentiation. *Ultrasound Obstet Gynecol* 42 (5) (2013) 596-602.

31. Danon O, Elmaleh M, Boukobza B, Fohlen M, Hadjnader K, Hassan M. Rhombencephalosynapsis diagnosed in childhood: clinical and MRI findings. *Magn Reson Imaging* 18 (1) (2000) 99-101.

32. Demaerel P, Kendall BE, Wilms G, Halpin SF, Casaer P, Baert AL. Uncommon posterior cranial fossa anomalies: MRI with clinical correlation. *Neuroradiology* 37 (1) (1995) 726.

33. Guibaud L, Larroque A, Ville D, Sanlaville D, Till M, Gaucherand P, *et al.* Prenatal diagnosis of « isolated » Dandy-Walker malformation: imaging findings and prenatal counselling. *Prenat Diagn* 32 (2) (2012) 185-93.

34. Torres-Mohedas J, Verdú A, Vidal B, Jadraque R. Joint presentation of facial hemangioma, posterior fossa malformation, and carotid-vertebral hypoplasia (Pascual-Castroviejo syndrome II): report of 2 new cases. *Rev Neurol* 32 (1) (2001) 504.

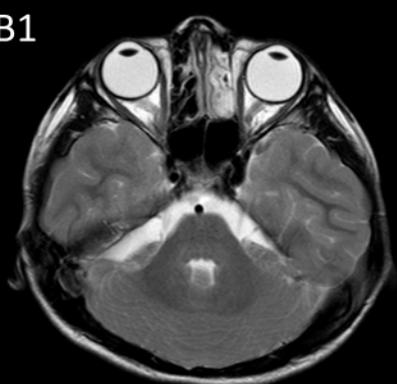
35. Bhattacharya A, Desarkar P, Haque S. A case of Dandy-Walker variant disorder associated with multiple neuropsychiatric comorbidities managed with behavioral therapy. *J Neuropsychiatry Clin Neurosci* 25 (3) (2013) E03-04.

36. Berquin PC, Giedd JN, Jacobsen LK, Hamburger SD, Krain AL, Rapoport JL, *et al.* Cerebellum in attention-deficit hyperactivity disorder: a morphometric MRI study. *Neurology* 50 (4) (1998) 108793.
37. Castellanos FX, Giedd JN, Berquin PC, Walter JM, Sharp W, Tran T, *et al.* Quantitative brain magnetic resonance imaging in girls with attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry* 58 (3) (2001) 28995.
38. Doyon J, Penhune V, Ungerleider LG. Distinct contribution of the cortico-striatal and cortico-cerebellar systems to motor skill learning. *Neuropsychologia* 41 (3) (2003) 25262.
39. Stoodley CJ, Valera EM, Schmahmann JD. Functional topography of the cerebellum for motor and cognitive tasks: an fMRI study. *Neuroimage* 59 (2) (2012) 156070.
40. Cortese S1, Kelly C, Chabernaud C, Proal E, Di Martino A *et al.* Toward systems neuroscience of ADHD: a meta-analysis of 55 fMRI studies. *Am J Psychiatry* 169 (10) (2012) 1038-55.
41. Truwit CL, Barkovich AJ, Shanahan R, Maroldo TV. MR imaging of rhombencephalosynapsis: report of three cases and review of the literature. *AJNR Am J Neuroradiol* 12 (5) (1991) 95765.
42. Guyot LL1, Kazmierczak CD, Michael DB. Adult rhombencephalosynapsis. Case report *J Neurosurg* 93 (2) (2000) 323-5.
43. Mendonca JLF, Natal MRC, Viana SL, Coimbra PPA, Viana MACB, Matsumine M. Rhombencephalosynapsis: CT and MRI findings. *Neurol India* 52 (1) (2004) 11820.
44. Chemli J, Abroug M, Tlili K, Harbi A. Rhombencephalosynapsis diagnosed in childhood: clinical and MRI findings. *Eur J Paediatr Neurol* (2007); 11 (1): 358.
45. Saugier-veber P, Marguet F, Vezain M, Bucourt M, Letard P, Delahaye A, Pipiras E, Frébourg T, Gonzalez B, Laquerrière A. Pontocerebellar hypoplasia with rhombencephalosynapsis and microlissencephaly expands the spectrum of PCH type 1B. *Eur J Med Genet.* (2020); 63(4):103814.
46. Massoud M, Guibaud L. Prenatal imaging of posterior fossa disorders. A review. *Eur J Paediatr Neurol.* (2018); 22(6): 972-988.

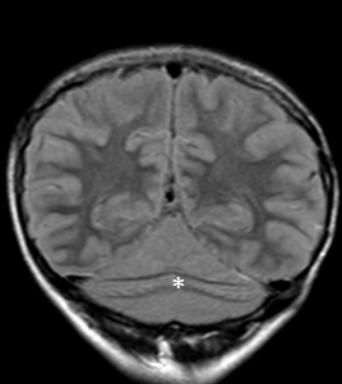
A1



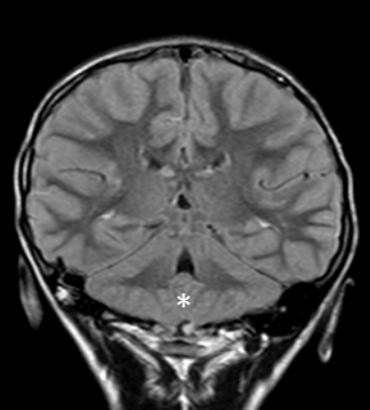
B1



C1



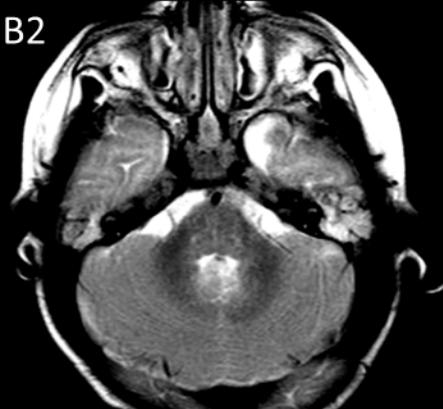
D1



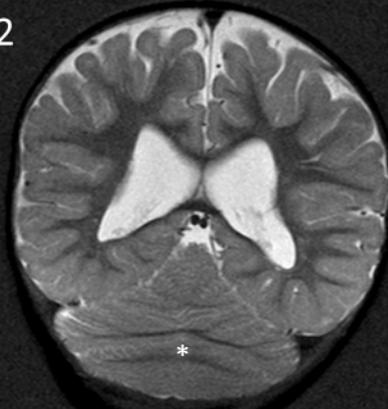
A2



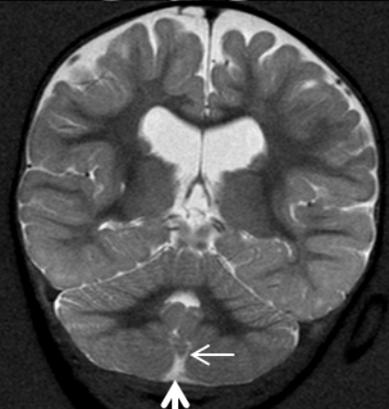
B2



C2



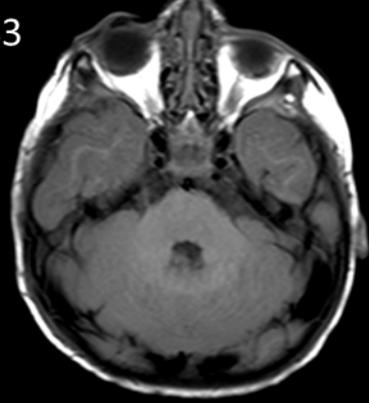
D2



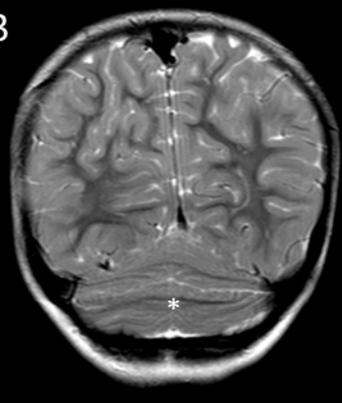
A3



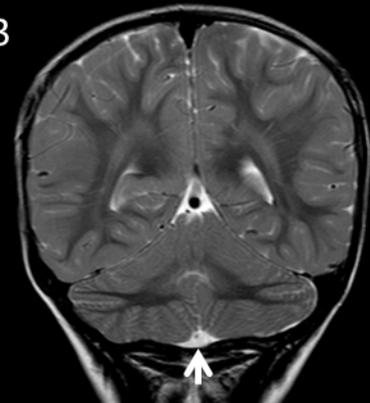
B3



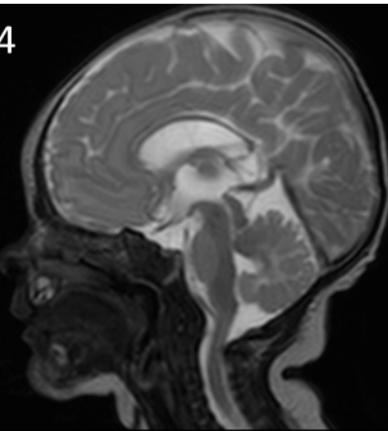
C3



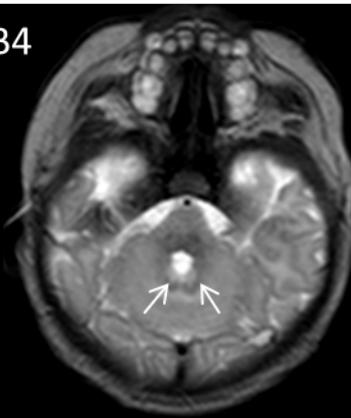
D3



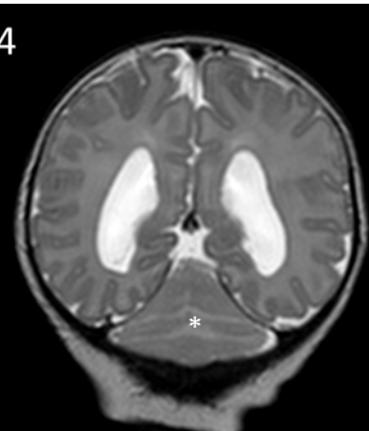
A4



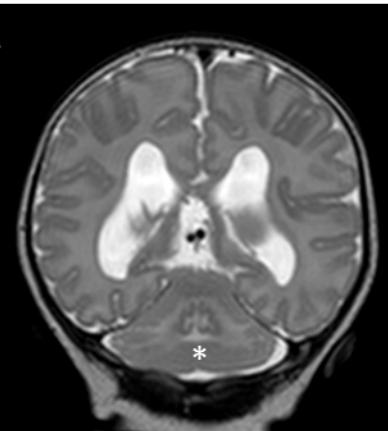
B4



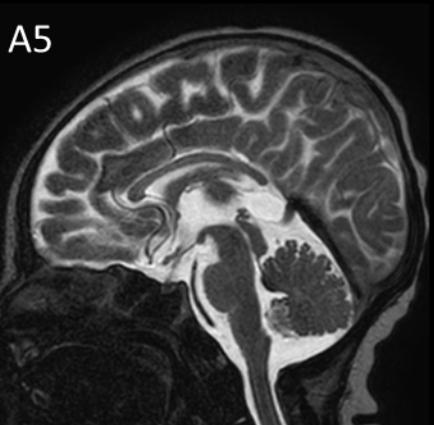
C4



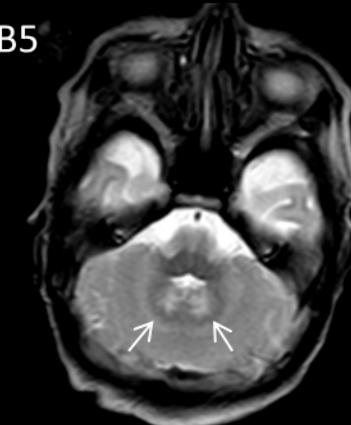
D4



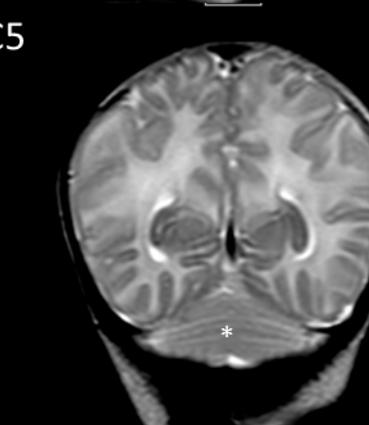
A5



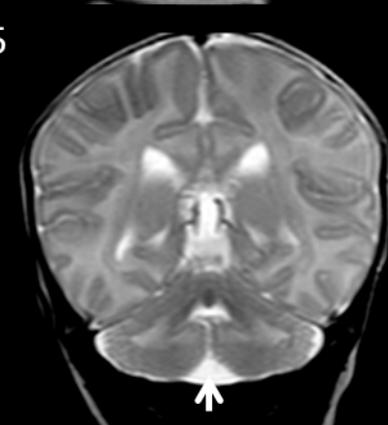
B5



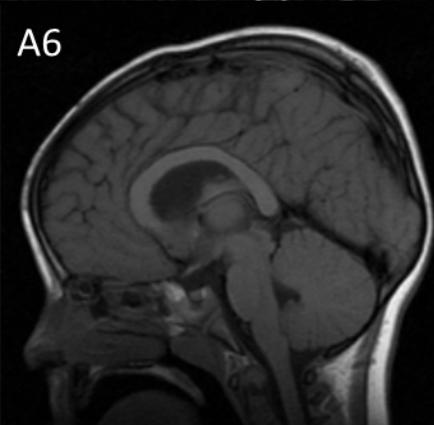
C5



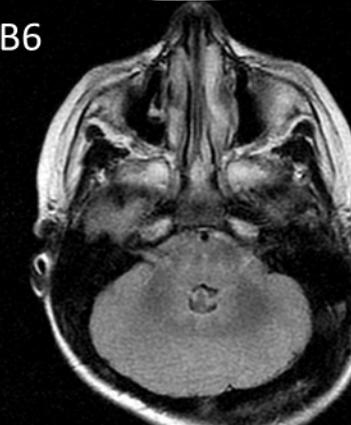
D5



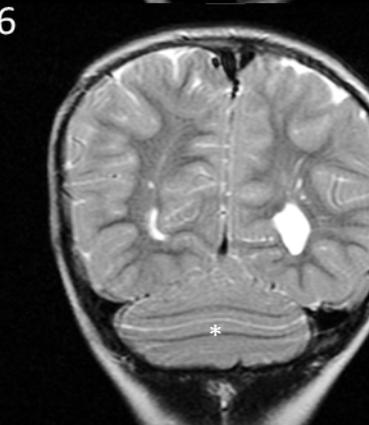
A6



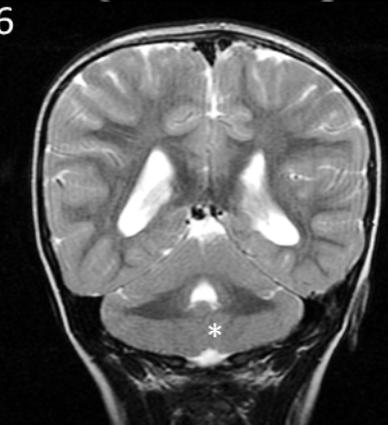
B6



C6



D6



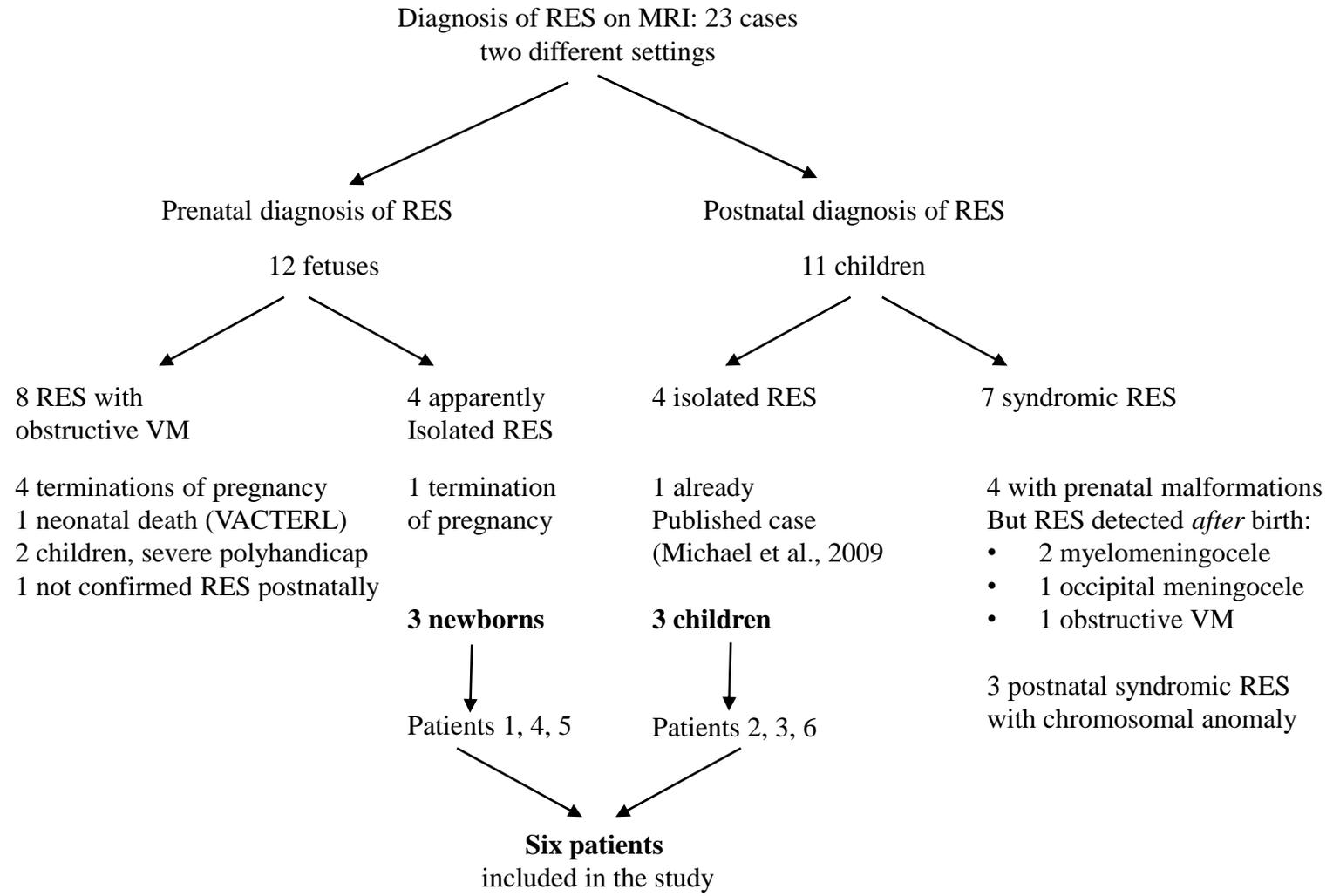
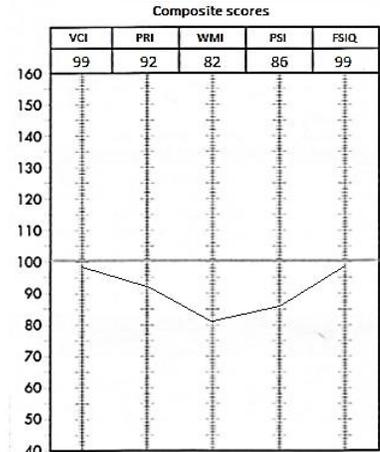
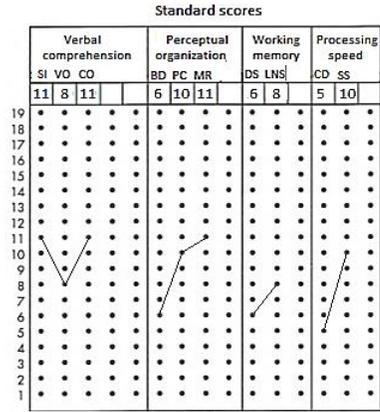
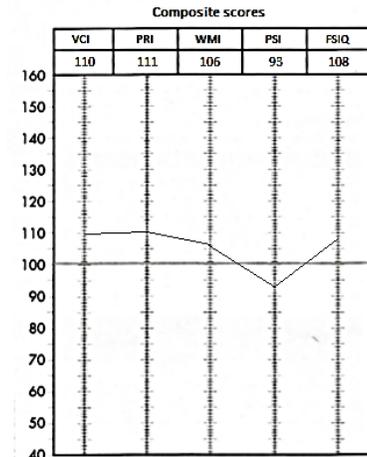
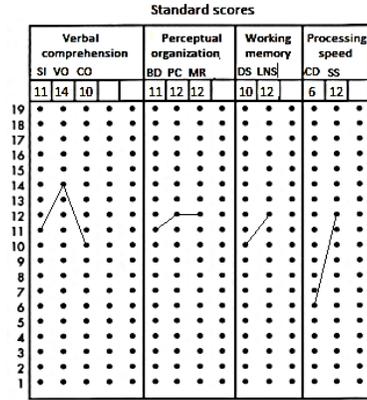


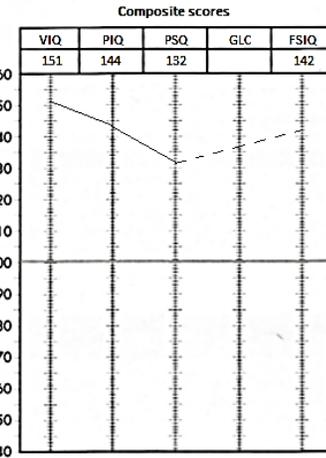
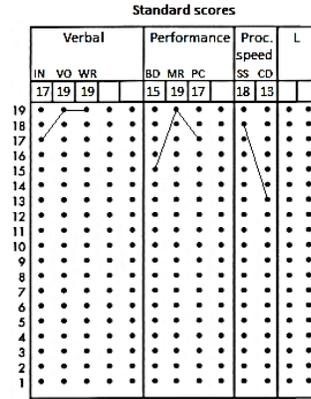
Figure 3.



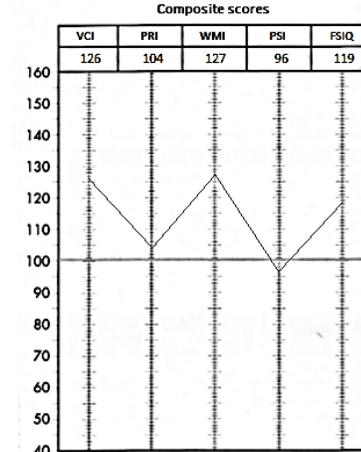
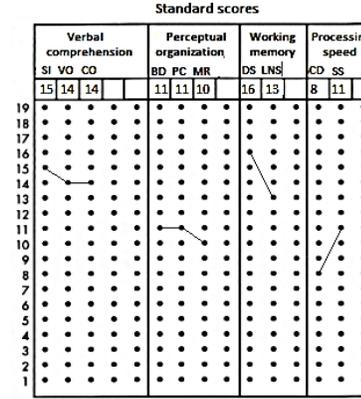
Patient 1 (WISC-IV)



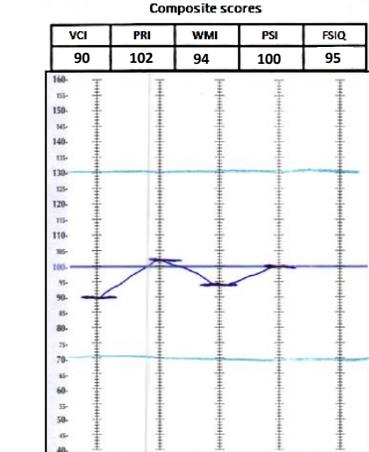
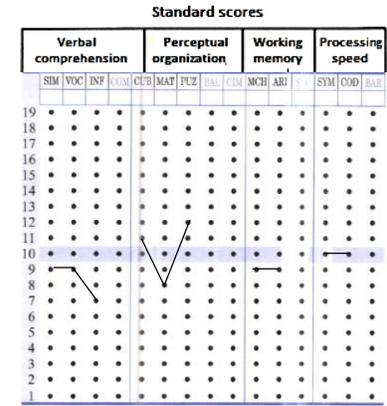
Patient 2 (WISC-IV)



Patient 3 (WPPSI-III)



Patient 4 (WISC-IV)



Patient 6 (WAIS-IV)

