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SPECIAL ANNUAL ISSUE

Chiari I malformation in defined genetic syndromes in children: are there common pathways?

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Abstract

Purpose Chiari malformation type I (CMI) is a common pediatric neurologic anomaly that can be associated with a variety of genetic disorders; however, it is not always clear whether the observed associations are real or random. The knowledge of the real associations could provide useful guidance to clinicians. Furthermore, it could be of help to better understand the still unknown genetic etiology of CMI.

Methods With the aim of implementing such insights, we retrospectively reviewed clinical, neuroradiological, and genetic data of patients harboring CMI evaluated at the Child Neurology Unit of our institution between January 2008 and December 2018.

Results The cohort consists of 205 patients (111 males and 94 females), with a mean age at diagnosis of 6.3 years (range 0–18 years). 188 patients completed an average follow-up period of 5.2 years (range one month–18 years). Mean age at last assessment was 11.4 years (range nine months–23 years). 127 (62%) children have been classified as syndromic due to the presence of neurodevelopmental disorders, phenotypic anomalies, or malformations. Among syndromic CMI children, a molecular diagnosis was identified in 35/127 (27.6%) (20 males and 15 females). The most common diagnoses were syndromic craniosynostosis in 8/35 children (22.9%), among which sevenare FGFR-related and one ERF-related craniosynostosis; disorders of the RAS/MAPK pathway, termed RASopathies or RAS/MAPK syndromes in 9/35 (25.7%); disorders of the PTEN-PI3K/AKT signal transduction cascade, termed PTENopathies in 3/35 children (8.6%); and chromosomal rearrangements in 6/35 patients (17.1%), two of whom with del16p11.2.

Conclusions We polarized our attention on the defined genetic diagnoses focusing not only on the phenotypic hallmarks but also on the phenotypic overlapping features. In addition, we discussed the pathophysiological mechanisms leading to progressive cerebellar ectopia and the involved molecular pathways. Along with the recent literature evidence, we suppose that interactions between FGFR and RAS/MAPK pathway and between RAS/MAPK and PTEN-PI3K/AKT pathways could explain some phenotypic overlapping features and could have a significant role in the pathogenesis of CMI.

Keywords Chiari I malformation · Genetic syndromes · RASopathies · Craniosynostosis · PTENopathies · Chromosomal rearrangements

Introduction

Chiari I malformation (CMI) is defined as cerebellar tonsillar herniation of ≥ five mm into the cervical canal, below the virtual line connecting the basion with the opisthion on sagittal brain or cervical spine magnetic resonance imaging (MRI) [13]. Its prevalence has been estimated between 0.24 and 3.6%, with higher estimates in children and young adults than in the elderly [24].

Despite the simple radiological definition, CMI is nevertheless a complex anatomical and clinical challenge that raises many debates on its definition, diagnostic criteria, classification, etiopathogenesis, and treatment [4].

Although it is usually diagnosed as an isolated anomaly in otherwise healthy subjects, it may occur in association with (a) cervico-medullary kinking and syringomyelia reported in up to 85% of CMI patients. The syrinx is secondary to cerebrospinal fluid (CSF) flow alteration due to the displacement of the

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cerebellar tonsils across the foramen magnum [47]; (b) skeletal anomalies, particularly of the cervical spine and cranio-vertebral junction such as Klippel-Feil anomaly, scoliosis, atlanto-occipital fusion, basilar invagination, retroversion of the odontoid process [41, 56]; (c) central nervous system malformations and space-occupying lesions, among those hydrocephalus, arachnoid cysts, brain tumors, myelomeningocele, and tethered cord [11, 16, 38, 55, 62]; (d) several clinical conditions including endocrinopathies, rickets, and craniosynostosis [9, 23, 29, 44, 54]; and (e) well-known genetic syndromes as Beckwith-Wiedemann and hemihypertrophy syndromes, Williams, Goldenhar, Crouzon, Costello, Kabuki, Noonan syndromes, Neurofibromatosis type I, and Ehlers-Danlos syndrome [8, 9, 12, 18, 19, 21, 22, 25, 29, 32, 35, 42, 45, 53, 55, 56, 59, 63].

In addition, acquired CMI has been reported secondary to ventricular and lumbar shunting procedures or chronic spinal leakage [5, 10, 43, 64].

Many etiopathogenetic theories have therefore been developed (the hindbrain dysgenesis and developmental arrest theory, the caudal traction theory, the hydrocephalus and hydrodynamic theory of Garner, and the lack of embryological ventricular distention theory), but none is exhaustive [29].

Currently, CMI is considered a heterogeneous and multifactorial anomaly that includes congenital and acquired forms, all due to an impaired balance between the cranial box (supratentorial cranial vault, posterior fossa) and intracranial contents (fore- and hindbrain). This impairment results in a deformation of the hindbrain so that Chiari I deformity is the correct term that should be used [41]. The congenital forms are considered to arise from a para-axial mesodermal disorder of the skull base, which determines underdevelopment of the posterior cranial fossa and downward displacement of the cerebellar tonsils [34]. Indeed, morphometric analysis of the posterior cranial fossa shows a shorter clivus with or without a shorter basiocciput, a smaller midsagittal area, and a larger tentorial angle [39, 61]. In contrast, in acquired tonsillar ectopia due to cranial hypertension, spinal hypotension, and cranial constriction, cranial fossa changes are not present.

The co-occurrence of CMI with known genetic syndromes and the familial aggregation support the hypothesis of a genetic contribution [48, 50]; however, genetic factors remain largely undetermined [30].

Several papers have focused on possible associations between CMI and genetic syndromes, but they have been mainly based on small clinical series, surgical series, or simple case reports. It is therefore not easy to understand whether the reported associations are real or random.

The knowledge of the real associations could have many important implications. It could allow clinicians treating CMI children to recognize signs and symptoms suggestive of associated genetic disorders and then to start the appropriate diagnostic workup. On the other hand, it might be useful for clinicians in the assessment of children with potentially CMI-associated genetic syndromes. Furthermore, it could be of help to better understand the still unknown genetic etiology of CMI.

With the aim of implementing the knowledge about the associations between CMI and genetic syndromes, we reviewed a cohort of children harboring CMI admitted to the Developmental Neurology Unit of our Institution. We polarized our attention on the defined genetic syndromes and the involved molecular pathways trying to clarify their interactions in the pathophysiological mechanism leading to the CMI development.

Clinical series

We retrospectively reviewed clinical, radiological, and genetic data of patients harboring CMI evaluated at the Developmental Neurology Unit of our institution between January 2008 and December 2018.

Our cohort consists of 205 patients (94 females and 111 males), with a mean age at diagnosis of 6.3 years (range 0–18 years).

The full list of indications leading to brain MRI evaluation is reported in Table 1. CMI diagnosis was often an unexpected finding during the neuroradiological evaluation of children with different neurodevelopmental disorders. All patients completed the neuroradiological workup with spine and cine MRI.

17 patients were lost at follow-up. 188 patients completed an average follow-up period of 5.2 years (range one month–18 years). Mean age at last assessment was 11.4 years (range 9 months–23 years).

Clinical evaluation included detailed familial and personal anamnesis, and physical and neurological examinations. For

Table 1 Clinical main indications leading to brain MRI

Indications	Patients	Percentage
Headache	63	30,7%
Psychomotor delay/Intellectual disability	32	15,6%
Autism spectrum disorder/ behavioral impairment	12	5,8%
Epilepsy	10	4,9%
Craniosynostosis	19	9,3%
Dysmorphic features/genetic syndromes	20	9,7%
Precocious puberty	4	1,9%
Growth hormone deficiency	9	4,5%
Papilledema	4	1,9%
ADHD, language impairment	6	2,9%
Other	26	12,6%
Total	205	

every patient, we explored the presence of craniofacial and dysmorphic features, growth anomalies, and congenital malformations.

Neuropsychological assessment was performed in all patients to analyze cognitive abilities and to evaluate behavioral and neurodevelopmental disorders such as autism spectrum disorders. Polysomnography, auditory brainstem, and somatosensory-evoked potentials were also carried out.

Based on clinical, neuroradiological, and neurophysiological results, we identified 78 (38%) patients with isolated or pure CMI and 127 (62%) clinically syndromic CMI children. Among the last group, appropriate genetic tests were carried out including Comparative Genomic Hybridization (CGH) Microarray, Sanger sequencing for specific genes or Next Generation Sequencing (NGS) panels for some phenotypic categories (as craniosynostosis), and methylation analysis for Prader Willi and Angelman locus.

A molecular diagnosis was obtained in 35/127 (27.6%) children (Table 2).

Table 2 Genetically confirmed diagnoses in 35 children with CMI

	Patients	(%)
Syndromic craniosynostosis	8/35	(22.9)
FGFR-related craniosynostosis		
Crouzon syndrome	*3*	
Pfeiffer syndrome	*2*	
Muenke syndrome	*2*	
ERF-related craniosynostosis	1	
RASopathies	9/35	(25.7)
Neurofibromatosis type 1	4	
Costello syndrome	2	
Noonan syndrome	3	
PTENopathies	3/35	(8.6)
PHTS	2	
MCAP	1	
Chromosomal rearrangements	6/35	(17.1)
del16p11.2	2	
del2p15	1	
dupXp22.31	1	
del5q14.3 (MEF2C haploinsufficiency)	1	
Potocki-Lupski syndrome	1	
Others	10/35	
Kabuki syndrome	1	
CHARGE syndrome	1	
Wiedemann-Steiner syndrome	1	
Prader-Willi syndrome	1	
Angelman syndrome	2	
Tuberous sclerosis complex	1	
Alport syndrome	1	
Raine syndrome	2	

The most common genetic syndromes were syndromic craniosynostosis in 8/35 children (22.9%), FGFR-related in sevenand ERF-related craniosynostosis in one patient; RAS/mitogen-activated protein kinase (MAPK) pathway disorders, termed RASopathies or RAS/MAPK syndromes in 9/35 (25.7%): neurofibromatosis type 1 in four cases, Noonan syndrome in three patients, and Costello syndrome in two children; tumor suppressor phosphatase and tensin homolog (PTEN) and phosphoinositol-3-kinase (PI3K)/vakt murine thymoma viral oncogene homolog (AKT) signal transduction cascade disorders, termed PTENopathies [33, 65] in 3/35 children (8.6%) among which two affected by PTEN hamartoma tumor syndrome (PHTS) and one with megalencephaly-capillary malformation syndrome (MCAP); chromosomal rearrangements in 6/35 patients (17.1%), two of whom with del16p11.2; and the remaining fourpatients respectively del2p15, dupXp22.31, del5q14.3 comprising MEF2C, and Potocki-Lupski syndrome.

Other genetic diagnoses included the following: Kabuki, CHARGE, Wiedermann-Steiner, Angelman, tuberous sclerosis, Alport, and Raine syndromes. All these diagnoses were detected in single patients except for Angelman syndrome and Raine syndrome. However, in this last case the patients were brother and sister.

Discussion

In this paper, we report on our cohort of children harboring CMI collected over the last decade, focusing on associated defined genetic diagnoses for both clinical and speculative purposes.

From a clinical point of view, the knowledge of which genetic syndromes are most frequently associated with CMI could represent useful guidance to clinicians. On the other hand, from a speculative point of view, identifying the relationship between CMI and genetic diseases could allow to better understand the etiology of CMI, which is still a matter of debate.

In our cohort, among 205 children with CMI, 127 (62%) have been classified as syndromic due to the presence of neurodevelopmental disorders, phenotypic anomalies, or malformations.

The high percentage of syndromic children can be explained by the characteristics of the recruiting medical center, which is dedicated in particular to the management of children with psychomotor delay or intellectual disabilities, neurodevelopmental disorders such as autism, neurocutaneous syndromes, and craniosynostosis. Often, the diagnosis of CMI represents an unexpected finding during the neuroradiological evaluation of children with different phenotypic and neurodevelopmental disorders.

Among syndromic CMI children, a molecular diagnosis has been identified in 35/127 (27.6%). The most common genetic diagnoses were syndromic craniosynostosis in 8/35 children (22.9%), RASopathies in 9/35 (25.7%), PTENopathies in 3/35 children (8.6%), and chromosomal rearrangements in 6/35 patients (17.1%).

Syndromic craniosynostosis and CMI

Craniosynostosis (CS), the premature fusion of one or more calvarian sutures, is a relatively common congenital malformation affecting one in 2100–2500 live births, but the prevalence is reported to be rising [17]. CS presents many challenges in classification, molecular genetic workup, and management due to its heterogeneous presentations and causes. It may involve a single suture or, rarely, multiple sutures, and may be isolated or non-syndromic (about 60–70% of cases), or associated with other congenital anomalies or clinical signs as part of a syndrome (about 30–40% of patients).

In the last three decades, significant progress has been made in understanding the genetic causes of CS represented by single-gene mutations or chromosomal rearrangements [17, 28].

In 2015, Twigg wrote a review comprising 57 human genes whose mutations are related to craniosynostosis [57]. After this work, 22 other genes have been identified [17].

A specific genetic diagnosis can currently be identified in a quarter of syndromic CS patients. However, non-syndromic patients are increasingly recognized as syndromic, even if the genetic causes of non-syndromic forms still remain largely unknown. At present, mutations in six genes account for three-quarters of all genetic diagnoses: *FGFR2*, *FGFR3*, *TWIST1*, *EFNB1*, *TCF12*, *ERF*. Mutations in the first four genes cause well-known and recognizable autosomal dominant syndromes: *FGFR2*, Apert, Crouzon, and Pfeiffer syndromes; *FGFR3*, Muenke and Crouzon with acanthosis nigricans syndromes; *TWIST1*, Saethre-Chotzen syndrome; and *EFNB1*, craniofrontonasal syndrome [17, 28].

Muenke, Crouzon, and Pfeiffer syndromes, diagnosed in two, three, and two children, respectively, in our cohort are the most frequent craniosynostosis syndromes; they are all due to activating mutations of FGFR genes.

Muenke syndrome, caused by a specific mutation in *FGFR3* (p.Pro250Arg), can present with an important inter- and intrafamily variability and has incomplete penetrance. It is characterized by coronal synostosis, midface hypoplasia, ptosis, down-slanting palpebral fissures, and minor digital anomalies; sensorineural hearing loss, developmental delay, and epilepsy can occur (Fig. 1).

Crouzon syndrome, due to *FGFR2* mutations, is characterized by craniosynostosis ranging from single-suture synostosis to pansynostosis, exorbitism, midface hypoplasia, and no digital anomalies.

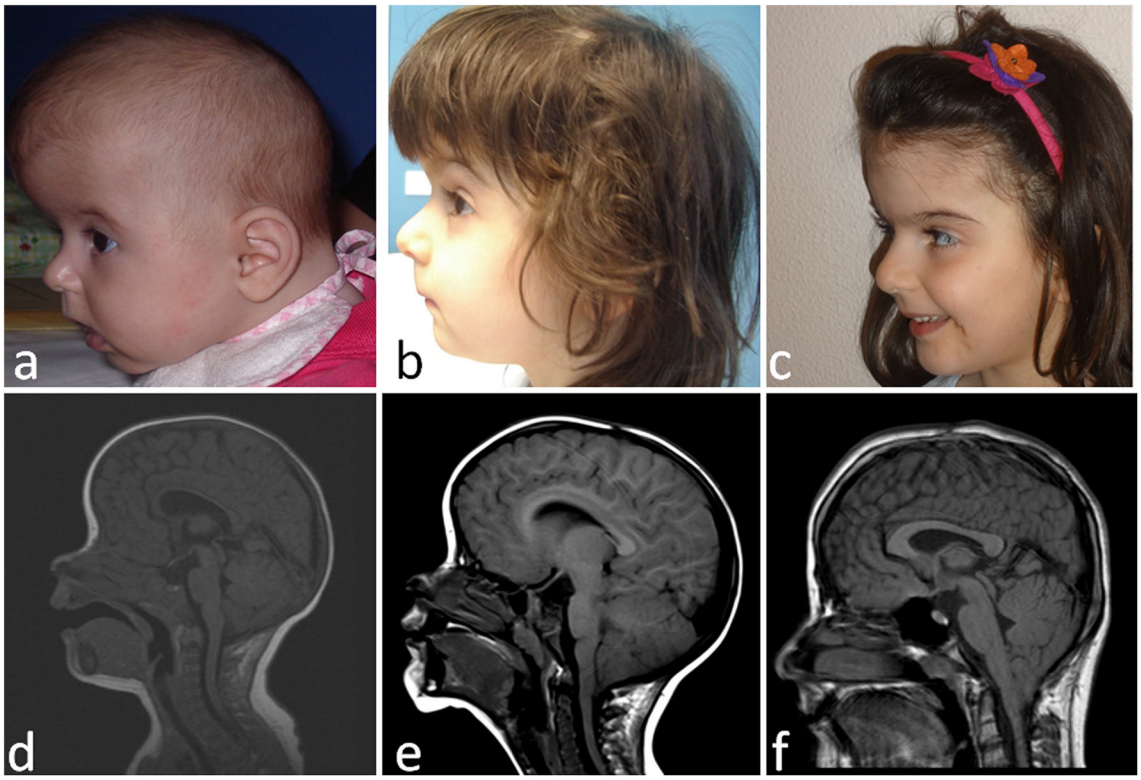

Fig. 1 Girl affected by Muenke syndrome. In **a**–**c**, the girl was three months, four years, and nine years old, respectively. She developed progressive tonsils ectopia up to CMI (**e**, **f**) despite surgery for craniosynostosis at the age of six months. The photos are reproduced with the permission of the child's parents

Pfeiffer syndrome is a genetically heterogeneous disease caused by heterozygous mutations in *FGFR1* and *FGFR2*. The expression is variable with multisutural CS and face anomalies similar to Crouzon syndrome; in addition, congenital airway malformations, deafness, cognitive impairment, radiohumeral synostosis, and hand and foot anomalies can be present [17, 31].

The risk of CMI in these syndromic CS is well known, but the prevalence, causes, and consequences are largely unclear. In a review article, Cinalli [7] reported the prevalence rates of 70% in Crouzon syndrome and 50% in Pfeiffer syndrome, contrary to the prevalence of 1.9% in Apert syndrome caused by specific gain-of-function mutations of *FGFR2*. Fearon too found a CMI in 23 of 28 (82%) patients with Pfeiffer syndrome [14]. At present, no reliable information is available about the prevalence of CMI in Muenke syndrome [31].

It has been shown that CMI in syndromic craniosynostosis is an acquired and progressive condition ascribed to the disproportion between hindbrain growth and abnormally small posterior fossa, as a consequence of the premature closure of the cranial base synchondrosis and the lambdoid sutures during the first two years [7]. Hydrocephalus co-occurs with tonsillar ectopia from 30 to 70% in Crouzon and Pfeiffer syndromes. As CMI develops earlier than the hydrocephalus, it has been supposed that the small posterior cranial fossa and the closure of the cranial base synchondrosis could cause herniation of the cerebellar tonsils and venous hypertension due to stenosis of the jugular foramen, which in turn may give rise to hydrocephalus [7].

Based on these studies, MRI screening for the presence of Chiari malformation in patients with Crouzon and Pfeiffer syndrome has been strongly recommended at the first evaluation, at the age of 4 years, and on clinical suspicion [31].

An ERF gene mutation has been identified in one male patient of our cohort affected by CS and CMI. *ERF*-related craniosynostosis was first reported in 2013 [58]. Currently, its prevalence in all syndromic CS is estimated at 2% and in clinically non-syndromic CS at 0.7% [15]. It appears to be associated mainly with sagittal and lambdoid synostosis (Mercedes-Benz pattern) but also with multisutural and pansynostosis. Clinical presentation of *ERF* mutations varies from a mild Crouzon-like picture with orbital hypertelorism, exorbitism, depressed nasal bridge, and mild malar hypoplasia to non-syndromic craniosynostosis. Importantly, synostosis starts in postnatal age; has an insidious, indolent, and progressive course with poor effects on head morphology; and results in raised intracranial pressure over the first few years with subsequent permanent visual impairments if children are not surgically treated. In addition, affected children are prone to develop CMI malformation, delays in language development, behavioral abnormalities, and mild learning disabilities [15].

Interestingly, *ERF* encodes a negative regulator of ERK 1/2, the key signal transducer at the base of the pathway from growth factor receptors through RAS-MAPK [58].

While *ERF* is a downstream molecule of the RAS signaling cascade, FGFRs are receptor tyrosine kinases that act upstream of the RAS/MAPK signaling pathway. It is, therefore, possible to infer that the overlapping Crouzon-like facial phenotypes of *FGFR* and *ERF* CS result from a shared downstream activation of the RAS/MAPK pathway [15].

RASopathies and CMI

RAS genes are well-studied cancer-related genes and play a central role in the RAS/MAPK pathway that controls many aspects of cell behavior, including proliferation, differentiation, and survival. Dysregulation in the RAS signaling cascade due to germline mutations in genes encoding components of the RAS/MAPK pathway leads to a specific family of malformation syndromes called RASopathies or RAS/MAPK syndromes [3].

These autosomal dominant disorders include neurofibromatosis type 1 caused by loss-of-function NF1 mutations; Noonan syndrome, caused by activating mutations primarily in *PTPN11*, *SOS1*, *RAF1*, and less frequently, in *KRAS*, *NRAS*, *BRAF*, *SOS2*, *RASA2*, *LZTR1*, *RRAS*, *RIT*, *SHOC2*, and *CBL*; Noonan syndrome with multiple lentigines caused by mutations in *PTPN11* and *RAF1*; capillary malformation-arteriovenous malformation syndrome, caused by haploinsufficiency of *RASA1*; Costello syndrome, caused by activating mutations in *HRAS*; Cardio-facio-cutaneous syndrome, caused by activating mutations in *BRAF* and *MAP2K1* (*MEK1*) or *MAP2K2* (*MEK2*); and Legius syndrome, caused by inactivating mutations in *SPRED1* [3].

Taken together, the RASopathies represent one of the largest known groups of developmental malformation syndromes, affecting approximately one in 1000 individuals. Each of the RASopathies exhibits a distinctive phenotype, but owing to the common underlying RAS/MAPK pathway dysregulation, these syndromes share numerous overlapping phenotypic features including a peculiar craniofacial appearance with absolute or relative macrocephaly, hypertelorism, downslanting palpebral fissures, epicanthal folds and ptosis, short stature, heart defects, cutaneous anomalies such as café-au-lait macules, lentigines and hyperpigmentation, variable neurocognitive impairment, and increased risk of developing both benign and malignant neoplasms [3].

In our cohort, among nine children with RASopathies, four were diagnosed with neurofibromatosis type I, three with Noonan syndrome, and two with Costello syndrome.

Several papers have provided evidence supporting the hypothesis of a link between CMI and RASopathies [12, 18, 19,

22, 25, 26, 35, 52, 53, 56, 63, 66]. In a retrospective review of his experience with 500 pediatric CMI, Tubbs reported the NF1 diagnosis in 5.4% of patients [56]; subsequently, he showed a concomitant CMI in 8.6% of 198 NF1 individuals who had brain imaging studies [53]. A number of case reports have also described CMI in Noonan syndrome, in Noonan syndrome with multiple lentigines, and in Cardio-facio-cutaneous syndrome [12, 22, 25, 66]. In patients with Costello syndrome, posterior fossa crowding with cerebellar tonsillar herniation has been noted in 27/28 (96%); cerebellar tonsillar herniation progressed in 10/17 (59%) with MRI follow-up, to become a Chiari I malformation in 32% of patients [18]. CMI in Costello syndrome has been attributed to progressive postnatal cerebellar growth [18, 19, 41]. As relative macrocephaly is common to all RASopathies, probably a similar mechanism of neuro- and abnormal gliogenesis resulting in megalencephaly may sometimes lead to the posterior fossa overcrowding and Chiari I malformations [41].

RASopathies and craniosynostosis: which link?

If the link between RASopathies and CMI is well known, it is now increasingly evident that there is a link also between RASopathies and craniosynostosis. Recently, one review and some reports describing craniosynostosis plus Noonan syndrome and Cardio-facio-cutaneous syndrome have outlined that individuals with RASopathies are at greater risk of craniosynostosis than the general population [1, 27, 51, 60].

Three children in our cohort, one affected by Costello syndrome and two by Noonan syndrome, underwent 3D-CT scans of the head that documented the sagittal suture synostosis (Figs. 2, 3, and 4). To date, no patient with Costello syndrome and craniosynostosis has been described. Altogether, our observations support previous evidence about a link between RASopathies and craniosynostosis.

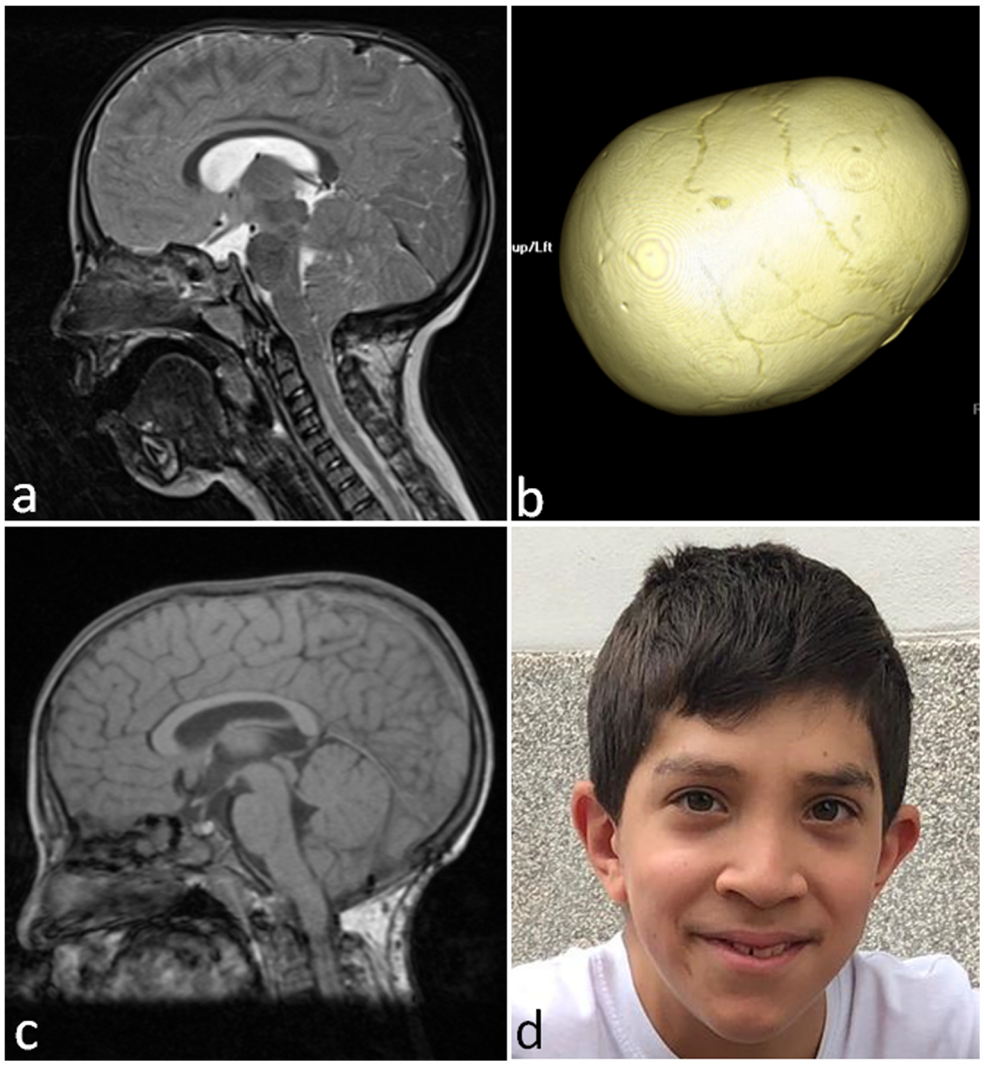

Fig. 2 A 13-year-old boy with Noonan syndrome. The first MRI (**a**: sagittal T2-weighted scan) shows CMI; the 3D CT scan (**b**) shows sagittal craniosynostosis. He underwent cranio-vertebral decompression for CMI at the age of seven years (**c**). The boy presents mild typical phenotypic characteristics of RASopathies: hypertelorism, down-slanting palpebral fissures, epicanthal folds, low-set ears. The photo is reproduced with the permission of the child's parents

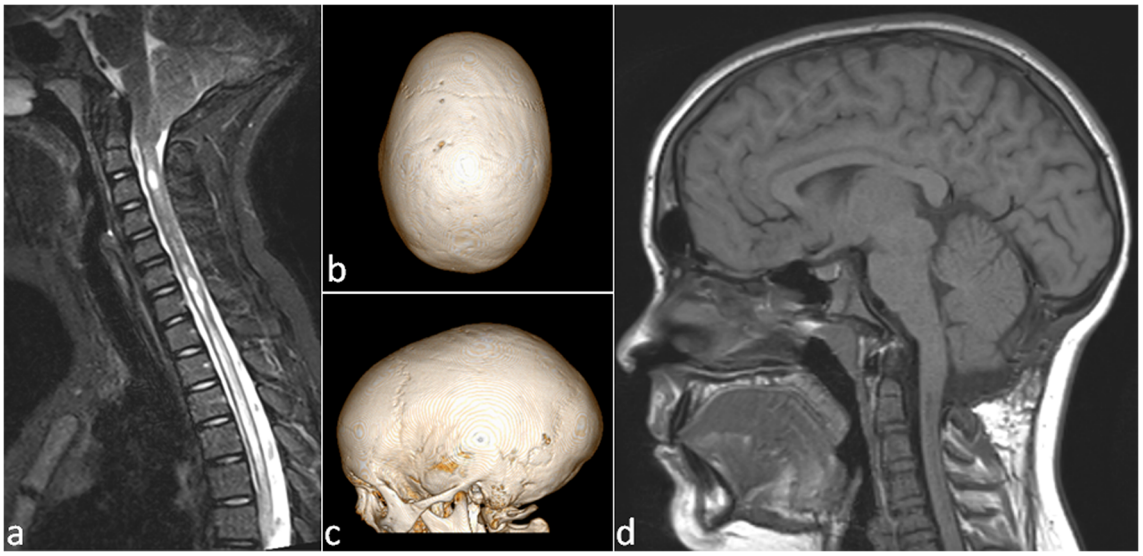

Fig. 3 Noonan syndrome with craniosynostosis and CMI with syrinx. Due to the onset of typical Chiari headache, this 14-year-old girl performed brain MRI, showing CMI and cervico-dorsal syringomyelia (**a** T2-weighted sagittal scan). The scaphocephalic head morphology suggested performing a 3D CT scan that revealed sagittal synostosis (b, **c**). After CMI surgery, cerebellar tonsils progressively ascended (**d** T1-weighted sagittal MRI scan)

The pathogenic mechanism by which craniosynostosis occurs in RAS/MAPK disorders remains unknown, but it is possible to speculate about the role of a possible interaction between the FGFR and the RAS/MAPK signaling pathways, with the RAS/MAPK pathway being a mediator of aberrant bone growth in cranial sutures [51]. Thus, not only megalencephaly but also dysregulated growth and/or suture closure might play a role in the etiopathogenesis of CMI as

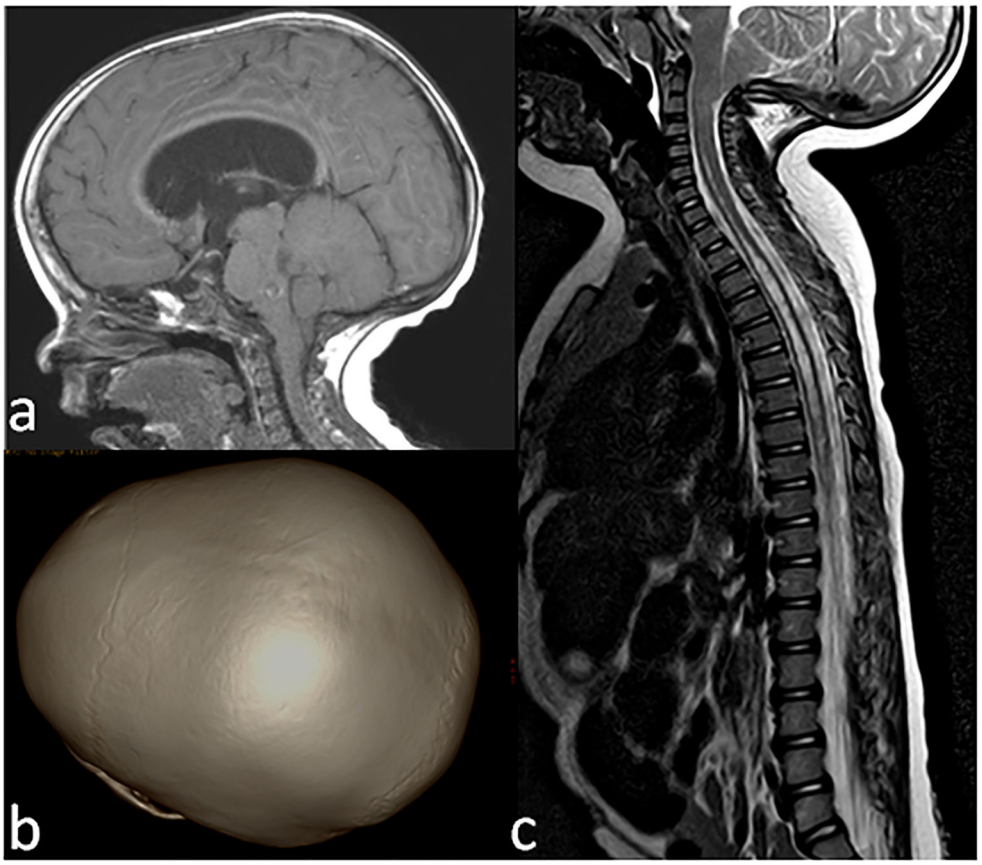

Fig. 4 Costello syndrome: a three-year-old girl with CMI, cervico-dorsal syrinx, and sagittal synostosis. The images show **a** cerebellar tonsils ectopia at the sagittal T1-weighted MRI scan, **b** the early closure of sagittal suture at the 3D CT scan, and **c** the cervico-dorsal syringomyelia at the spinal T2-weighted MRI sagittal scan

well as in RASophaties craniofacial anomalies [27]. The small number of reported patients with the association RASopathy-CMI-craniosynostosis does not allow us to draw up recommendations about when and how often neuroimaging studies should be performed.

PTENopathies and CMI

Extreme macrocephaly is also the cardinal feature of the so-called PTENopathies, another group of genetically defined disorders of our cohort. PTEN is a tumor sup-

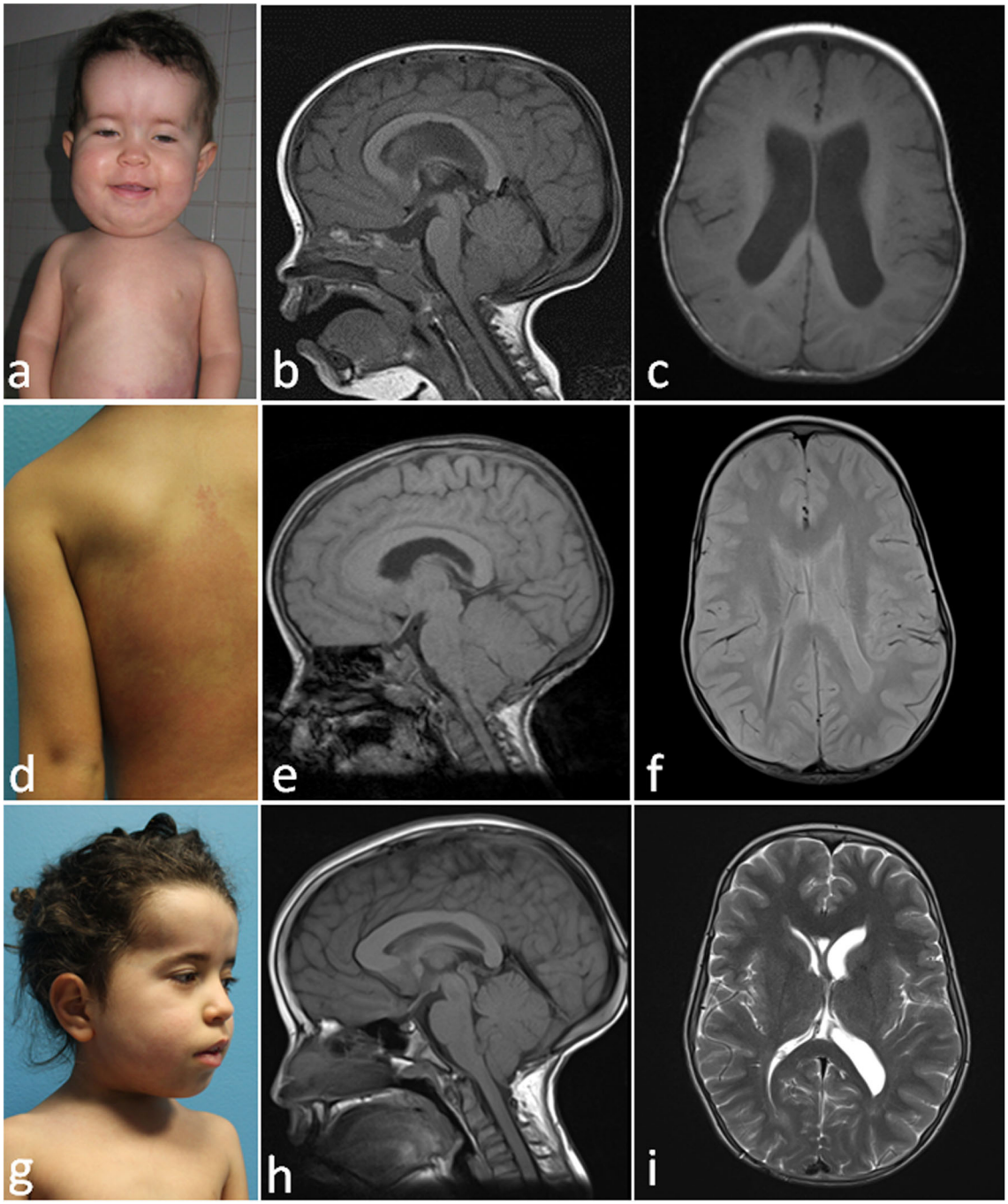

Fig. 5 Phenotypic and radiological evolution of a girl with MCAP. **a** shows the girl at the age of 12 months with the corresponding sagittal and axial T1-weighted MRI scans in **b** and **c**. Megalencephaly is visible as well as CMI. In **d**, detail of dorsal region of the child at 24 months of age with the typical cutaneous capillary malformation. The sagittal (**e**) and axial (**f**) MRI scans performed at that age,six months after ventricular peritoneal shunting, depict ventricular size reduction with persistent cerebellar tonsils descend. Ventricular size reduction is more evident at MRI performed at the age of nine years old (**h**, **i**) with persisting CMI despite posterior fossa decompression at two years and 10 months of age. In **g**, the facial characteristics of the girl when she was nine years old. The photos are reproduced with the permission of the child's parents

pressor gene, whose pathogenic heterozygous germline mutations are implicated in familial cancer predisposition, such as Cowden and Bannayan-Riley-Ruvalcaba syndrome, in Proteus and Proteus-like syndrome, malformation syndromes with segmental overgrowth associated or not with intellectual disability as well as in children with macrocephaly and autism or developmental delay/cognitive impairment. PTEN hamartoma tumor syndrome (PHTS) is the umbrella term used to comprise the spectrum of these disorders, regardless of the phenotype [33]. As timely diagnosis is crucial for medical and developmental surveillance, as well as for testing other at-risk family members, it is vital to know that extreme macrocephaly (occipitofrontal circumference > 2 standard deviations over the population mean, or 97.5th percentile) and neurodevelopmental disorders are well-established presenting clinical features in children, whereas cancers and polyps are common presenting symptoms in adults [20].

Previously, reviewing our cohort of 16 PHTS children, we described that 37% had a downward displacement of the cerebellar tonsils through the foramen magnum and two of them (12%), reported also in this study, had tonsillar descent greater than five mm that required surgical corrections for syringomyelia [6, 46].

PTEN gene encodes a protein with a dual phosphatase activity: it inhibits the MAPK signaling pathway, and it antagonizes the PI3K/AKT signal transduction cascade. This is a cellular pathway that, as RAS/MAPK, regulates cell growth, proliferation, metabolism, survival, apoptosis, angiogenesis, tumorigenesis, and brain development. Consequently, *PTEN* loss of function leads to dysregulation of these pathways, thus explaining PHTS phenotypes such as overgrowth and malignancy [33].

Gain-of-function germline and somatic mosaic mutations in genes (AKT1, AKT3, PIK3CA, PIK3R1, and PIK3R2) encoding components of the PI3K/AKT pathway downstream of *PTEN* also predispose to syndromes with partially overlapping clinical manifestations, mimicking loss-of-function effects of *PTEN*. These syndromes reported as PTENopathies [33, 65], comprise overgrowth disorders affecting the body or the brain as megalencephaly-capillary malformation syndrome (MCAP) diagnosed in one patient of this study [37].

MCAP is characterized by congenital or early postnatal megalencephaly, with a high risk for progressive ventriculomegaly leading to hydrocephalus, large cerebellum leading to posterior fossa crowding, and progressive cerebellar tonsillar ectopia to Chiari malformation, reported by Mirzaa respectively in 15 and in 18/21 children [36] (Fig. 5). MCAP is further characterized by cortical brain abnormalities, distinct cutaneous capillary malformations, finger anomalies such as syndactyly and postaxial polydactyly,

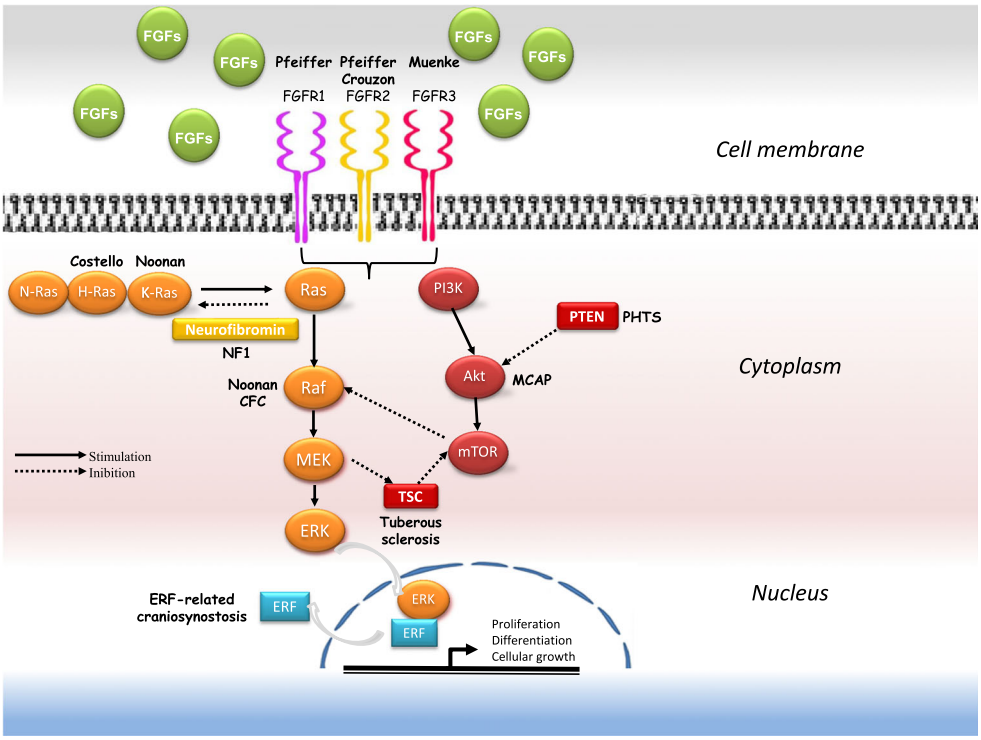

Fig. 6 Schematic representation of interactions among FGFR, RAS/MAPK, and PI3K/AKT pathways. The names of the corresponding syndromes are reported close to the specific genes of the pathways

variable connective tissue dysplasia, and mild focal or segmental body overgrowth [37].

Chromosomal rearrangements and CMI

Other defined genetic syndromes associated with CMI are represented in this study by chromosomal rearrangements (17.1%) detected by array-based Comparative Genomic Hybridization (a-CGH), which can find microscopic and sub-microscopic copy number variants (CNVs). During the last years, thanks to this technique, several patients with intellectual disabilities and/or malformation anomalies have been diagnosed to be affected by chromosomal microdeletions or microduplications and their genetic anomalies have been recognized as distinct syndromes.

Among chromosomal rearrangements, del16p11.2 has been diagnosed in this study in two unrelated children with CMI.

Deletions and duplications of the recurrent ~ 600-kb BP4-BP5 region on chromosome 16p11.2 are among the most frequent genetic etiologies of autism spectrum disorder (ASD) and are associated with a wide spectrum of behavioral abnormalities [49]. It has been shown that individuals with 16p11.2 deletions have signs of overgrowth in the posterior fossa with a high likelihood of cerebellar tonsillar ectopia (30.7%) and Chiari I malformations in a significant percentage of cases (9.3%) [40].

Other genetic syndromes and CMI

The remaining patients of our cohort had a diagnosis of Angelman, Kabuki, Wiedemann-Steiner, Prader-Willi, Alport, Raine, and CHARGE syndromes and tuberous sclerosis.

For some of these syndromes, such as Kabuki syndrome [8, 32], the association with CMI has already been reported and is probably not coincidental, while to our knowledge, for other ones (such as Prader-Willi) the association has not been reported.

Interestingly, two unrelated patients in this series are affected by Angelman syndrome (AS), in both cases due to pathogenic variants of *UBE3A*. AS is characterized by severe developmental delay, lack of speech, autistic features, gait ataxia and/or limb tremors, seizures, and a unique behavior with frequent laughter, smiles, and excitability. Microcephaly with flat occiput and occipital groove are also common. In MRI studies, the brain usually appears structurally normal, although mild cortical atrophy or delayed myelination, white matter volume reduction, and focal white matter signal abnormalities may be observed [2]. To our knowledge, CMI has never been reported in association with AS. The association in our series may, therefore, be accidental. However, brain MRI is not considered a useful test in the diagnostic process and in the management of children with Angelman syndrome. Consequently, it is possible that the ectopia of the cerebellar tonsils may be present in a number of individuals.

Conclusions

In our clinical series of syndromic CMI children, FGFR-craniosynostosis, RASopathies, PTENopathies, and chromosomal rearrangements represent the most frequent associated genetic disorders. Based on our experience, we think that during the clinical evaluation of a child with CMI, some red flags should be considered in order to make a correct diagnosis and medical management. Particular attention must be paid to the presence of macrocephaly, skull deformities, dysmorphic facial features such as hypertelorism and down-slanting palpebral fissures ("Noonan-like" features), skin pigmentation anomalies, family history of cancers, as well as of course, developmental delay and cognitive disorders. On the other hand, clinicians who encounter children with syndromic craniosynostosis, RAS/MAPK disorders, PTENopathies, and some distinct syndromes should be alerted about the possibility of progressive cerebellar tonsils herniation to CMI.

In conclusion, CMI may be the common expression of a wide variety of pathologies; the multiplicity and diversity of associated clinical conditions suggest a multidisciplinary clinical approach to patient care and a careful neurological examination should always be included; the identification of a genetic relationship between associated diseases can help to understand the etiopathogenesis of CMI.

Interestingly, our cases, along with literature evidence, suggest interactions among FGFR-RAS-PI3K pathways that could explain some phenotypic overlapping features and could have a significant role in the pathogenesis of CMI (Fig. 6).

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Informed consent Informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

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