Chiari I malformation, syringomyelia and papilledema: a malformative complex connected to oculo-auriculo-vertebral spectrum

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Abstract

The authors discuss the association of papilledema with Chiari I malformation (CMI) and syringomyelia on the basis of a clinical case studied by radiology, immunology and biochemistry methods. In the presence of normal haematology, blood immunology and biochemistry, clinical signs of headache and papilledema associated to hemifacial asymmetry, blind neck fistulas, malformed ears and spinal abnormalities (symptoms of oculo-auriculo-vertebral spectrum - OAVS), were observed. Magnetic resonance images and computed tomography demonstrated the occurrence of lowered cerebellar tonsils, but with values lower than those typical of the CMI syndrome and syringomyelia. The authors concluded for a minor form (*benign ectopia*) in the CMI syndrome, associated to papilledema and syringomyelia, and hypothesize an unique pathogenetic mechanism for this complex, connected to neural crest cell development and to OAVS, as extension of this spectrum. The authors underline the relevance of the facial/neck lateral signs for the diagnosis of OAVS associated to brain stem pathology and CMI.

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Introduction

The association of papilledema with Chiari I malformation (CMI) and syringomyelia has been rarely reported and the pathogenesis of this complex is not completely understood: it is thought to be a complex malformation connected to oculo-auriculo-vertebral spectrum (OAVS), a neural crest cells (NCC)-derived disease.

Michaud and Sheridan[1] reported the association of Goldenhar syndrome (at present considered a particular form of OAVS) with CMI and syringomyelia; subsequently, Inci and Sağlam[2] reported about this association in another patient. Papilledema was also reported in CMI[3] and discussed in Goldenhar syndrome by Kirkham.[4]

Here we report and discuss the association of CMI with syringomyelia and papilledema, and the possible relationships with OAVS.

Materials and Methods

Haematological, biochemical, endocrinological and immunological tests were carried out by common laboratory methods.

Motor Evoked Potentials were evaluated after transcranial magnetic stimulation and recorded from the opponens pollicis during 30% of maximal contraction, according to standard methods. Somato Sensory Evoked Potentials (SSEPs) were recorded after stimulation of median nerve at wrist. Active electrodes placed over the sixth cervical vertebra were utilized to evaluate spinal responses, placing reference electrodes over thyroid cartilage; the same placement (reference electrodes over thyroid cartilage) was utilized to record peripheral nerve potentials from Erb's point. SSEPs were recorded after stimulation of tibialis nerve at ankle by standard techniques. Cortical responses were recorded from the parietal scalp.

Magnetic Resonance Images (MRI) were acquired by standard methods.

The evaluation was carried out on a female patient who was followed from infancy to date.

Results

None of relatives of the patient suffered from neurological or ophthalmological problems. The patient complained from infancy of headache episodes, some with aura and other without aura, with normal EEG. From 24 years of age, she suffered from myopia (right eye -1.75; left eye -3.25), which was corrected with spherical lenses, and from retro-orbital and sub-occipital pain, exacerbated by Valsalva manoeuvre. Eye consultation showed normal papilla, retinal and visual fields, tone and ocular motility.

At 26 years of age, she suffered from daily episodes of vertex headache associated to ocular phenomena (amaurosis preceded by sparking scotomata at the right eye, interesting subsequently the left eye) and to desultory paresthesias at the right hemisoma, dysarthria and confusion. These symptoms were treated with analgesics and tryptans with slight results.

At 30 years of age, the patient showed facial asymmetry (left hemiface<right), bilateral microtia, and abnormal ear lobule with Darwin tubercle; she showed blind skin fistulas (branchial clefs residual) at left side of neck (Figure 1). Neurological examination showed decreased osteo-tendineous (OT) reflexes on the left upper extremity, but hyperactive ones on the lower limb. Cranial nerves and gait were normal. Ophthalmological examination showed bilateral papilledema and ocular fields bilaterally restricted, mainly on the left side.

MRI showed relatively lowered cerebellar tonsils, asymmetry (left<right) of cerebral lateral ventricles, tiny hyperintensity of perivascular gliosis in subcortical white matter of both hemispheres and pons, and venous dysplasia with little angioma in white matter below the right ventricular horn. Angio-MRI demonstrated thin left sinus transversus, jugular sinus and jugular vein, as well as asymmetry of the lateral venous sinuses (left<right) with abnormal insertion of the superior longitudinal sinus on the lateral right sinus. Carotid Doppler was normal. Lumbar puncture showed high pressure (220 mm H_2O) of Cerebro Spinal Fluid (CSF); haematological, serological, biochemical and cytological values were normal (Table 1).

Pseudotumor cerebri associated to venous Central Nervous System abnormalities, headache, analgesics and tryptans intoxication were diagnosed.

At 30 years and 8 months of age, after subtraction of 11 ml of CSF, acetazolamide was started and continued for three months with improvement of headache. At 31 years, hormonal and immunological tests were normal (Tables 2 and 3). Neoplasia and autoimmune diseases were excluded according to Fornaro *et al*.[5,6]

Neuro-ophthalmological consultation showed mild sectorial papilledema at left eye, normal right fundus, and reduced visual fields (left>right). On this basis, a possible opticopathy was suspected. At 31 years and 8 months of age, a second CSF evaluation demonstrated raised pressure (250 mm H_2O); 7 mL of CSF were subtracted, resulting in final pressure of 160 mm H_2O.

Furosemide therapy was started and continued in following days. Visual Evocated Potentials showed signs of abnormality of stimulus conduction evidenced by reduced amplitude and raised latency on left side (a condition induced by optical nerve pathology). Headache persisted, mainly at the right side. Romberg sign was present. At 32 years of age, before surgery, haematological, biochemical, hormonal (Tables 1-3), and cardiological (Table 4) tests were normal; a subarachnoideal-spinal/peritoneal shunt (lumbo-peritoneal shunt) was done in order to lower CSF pressure.

The patient felt well, without headache during six months; haematological, biochemical, and hormonal tests were normal (Tables 1 and 2). Thereafter, an episode of tachycardia, raised arterial pressure, short breath, left arm pain with subsequent numbness of the left arm, was reported. ECG and cardiology were normal. Thyroid hormones and cathecolamines were in normal range (Table 2). Radiology showed some flexions of the catheter; Computed Tomography (CT) demonstrated low position of cerebellar tonsils. The episode spontaneously resolved.

At 34 years, cerebral MRI demonstrated normal ventricular volume; cerebellar tonsils were relatively lowered having tip at level of foramen magnum (Figure 2). Myelo-MRI showed expansion of spinal chord from D8 to D10 with a cystic intramedullary dorsal structure, including the central canal and containing a fluid similar to CSF (Figure 3). Syringomyelia with hydromyelia were diagnosed. Anti-aquaporin 4 antibodies were negative (Table 3). Rachis MRI showed reduced normal lumbar lordosis, with disc protrusion at D9-D10, and at L2-L3; disc bulging at L3-L4 and L4-L5. Routine tests were normal. Visual fields, ocular pressure and papilla were unaltered. Headache ameliorated. At 34 years 6 months the previous MRI at the foramen magnum level was confirmed (Figure 4).

At 35 years 11 months, the patient presented neck pain irradiated to face and left hemisoma after neck flexion, followed by vomit, dysarthria, and falling. This episode lasted 30 minutes and was followed by numbness. The symptoms resolved after placing the patient in horizontal position for 48 hours; the patient sensed shunt discharge in peritoneum and slight abdominal pain. Lactacidemia was 20 mg/dL (normal values 10-19 mg/dL). Neurophysiological tests demonstrated normal central motor conduction velocity time (assessed by cortical stimulation) on right side; on the left side tibialis anterior laevus raised latency was present (31.1 ms by cortical stimulation; 13.5 ms by radicular stimulation; TCCM = 17.6), as expression of cortico-spinal dysfunction. SSEPs by median nerve stimulation on wrist resulted in normal cervical responses, central conduction time, cervical responses latency, and

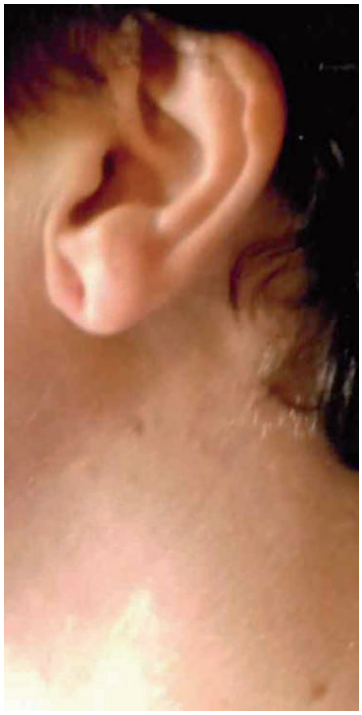

Figure 1. Occurrence of microtia, abnormal ear lobule, Darwin tubercle, blind skin fistulas at left neck in the patient.

cortical response latency, bilaterally. After tibial nerve stimulation on ankle the cortical response of reference peak P40 showed bilateral SSEPs latency delay (44.8 ms on right and 46.8 ms on left). Morphology and amplitude of potentials were normal. These results were compatible with syringomyelia (Table 5). At 36 years of age a new episode of pain was signalled; CT showed further descent of cerebellar tonsils.

Discussion and Conclusions

In summary, at MRI the patient presented low cerebellar tonsils, not more than 5 mm below of the occipital foramen, associated to episodes of vertex and sub-occipital pain, headache, raised by Valsalva manoeuvre, pseudotumor cerebri with raised CSF pressure and scotomata, retro-orbital pain in the presence of normal haematological, biochemical, immunological and hormonal tests, as already reported by Milhorat *et al.*[3]

The placement of a lumbo-peritoneal shunt caused partial disappearance of symptoms, according to Sullivan *et al*.,[7] but subsequently they re-appeared associated to tachycardia, raised arterial pressure, concomitant to a geniculation of the lumbo-peritoneal catheter. Similar symptoms were reported in another occasion, after head flexion, as already reported by Tubbs *et al*.[8] Recently, descent of cerebellar tonsils more than previously observed was demonstrated by CT. After shunting, syringomyelia was showed. A diagnosis of CMI syndrome was considered, based on clinical symptoms.

Table 1. Hematological and blood biochemistry values at different age of the patient.

Hematology	Age			Normal values
	30 y 4 m	32 y (before surgery)	32 y 4 m (after surgery)	
White cells/mm^3	9650	7360	n.d.	4000-10000
Red cells/mm^3	5090000	5080000	n.d.	4000000-5500000
Haemoglobin (g/dL)	14.9	14.7	n.d.	12-16
Platelets/mm^3	312000	257000	n.d.	150000-400000
Neutrophils (%)	69.9	69.1	n.d.	55-70
Lymphocytes (%)	23.7	25.0	n.d.	25-48
Monocytes (%)	3.3	5.0	n.d.	1-13
Basophils (%)	0.4	0.1	n.d.	0-1.5
Eosinophils (%)	1.3	0.8	n.d.	1-5
Blood biochemistry				
Azotaemia (mg/dL)	20.0	20.0	n.d.	10-50
Glycaemia (mg/dL)	104.0	94.0	97.0	70-110
Creatinine (mg/dL)	0.77	0.6	0.6	0.5-1.1
Na (mEq/L)	138	135	136	135-145
K (mEq/L)	4.2	4.2	4.0	3.5-4.5
Cl (mEq/L)	103	n.d.	n.d.	96-105
pH	7.38	n.d.	n.d.	7.35-7.45
Venous pCO_2 (mmHg)	30.5	n.d.	n.d.	30-35
Excess Bases (mmol/L)	-5.7	n.d.	n.d.	±2
Bicarbonate standard (mEq/L)	16.0	n.d.	n.d.	22-29
Glutamic Oxalacetic Transaminase (UI/L)	19	28	14	0-31
Glutamic Pyruvic Transaminase (UI/L)	20	33	17	0-30
γ-Gamma Glutamyl Transferase (UI/L)	20	13	20	5-36
Alkaline phosphatase (UI/L)	79	75	63	35-105
Pseudocholinesterase (UI/L)	10407	9361	5320	5320-12920
Creatin Phospho Kinase (UI/L)	82	63	63	10-140
C Reactive Protein (CRP) (mg/dL)	4	0.17 (n.v. <0.5)	n.d.	0-5
Total cholesterol (mg/dL)	184	199	190	130-200
High Density Lipoprotein cholesterol (mg/dL)	n.d.	57	63	65-80
Low Density Lipoprotein cholesterol (mg/dL)	n.d.	123	102	<140
Tryglycerides (mg/dL)	112	97	114	30-200
Proteins (g/dL)	7.2	7.2	n.d.	6-8
Lactic Dehydogenase (UI/L)	n.d.	202	n.d.	135-214
Red cells sedimentation rate (mm/hour)	30	15	4	0-20

CMI is characterized by cerebellar tonsil descent at least 5 mm below the foramen magnum,[3] as demonstrated by T1-weighted MRI, but some patients at surgery presented lower tonsillar descent, even though accompanied by clinical symptoms of CMI.[8]

At present, CMI is considered to be due to a disproportion between the underdeveloped posterior cranial fossa and the brain stem, with compression of the hindbrain, consequent descent of cerebellar tonsils[3,9] and CSF flow disturbances. Brain stem compression and fluid disturbances are responsible of headache, neck pain, pseudotumor-like symptoms and of the possible hydrocephalus, syringomyelia and compression of other nervous tissues.[3]

Not all patients with CMI exhibit tonsillar herniation of 5 mm or more: out of 364 patients reported by Milhorat *et al*.[3] with this syndrome, 32 exhibited tonsillar descent less than 5 mm (*benign tonsillar ectopia*)[8], but they were diagnosed as having CMI due to typical symptoms.

Oakes[10] and Tubbs *et al*.[8] reported that 50-75% of patients with CMI showed syringomyelia. On the basis of these reports, the diagnosis of CMI may be possible in the absence of 5 mm tonsillar descent, if syringomyelia is present and associated to clinical symptoms of CMI.[3,8] In these patients, decreased velocity flow in the cisterna magna, cisterna pre-pontina, pre-medullary spaces and in subarachnoid spaces were reported.[3]

The CMI anomaly may be sporadic, autosomal dominant or recessive trait[3,11] in some families, or may be associated to osteochondrodystrophies.[12]

The frequent association between CMI and syringomyelia induced to consider CMI as a leading cause of syringomyelia.[3,8]

Ball and Dayan[13] stated that in communicating syringomyelia

Table 2. Hormones and their metabolites in blood and urine of the patient.

Blood Hormones	Age 30 y 4 m	31 y (before surgery)	32 y 4 m (after surgery)	32 y 6 m (after pain episode)	Normal values
FT3 (pg/mL)	3.3	2.85	n.d.	n.d.	1.8-4.2
FT4 (pg/mL)	13.8	12.6	n.d.	10.9	8.0-19.0
Thyroid-Stimulating Hormone (TSH) (µU/mL)	2.12	0.88	n.d.	1.62	0.5-4.4
Prolactine (ng/mL)	32.41	17.0	n.d.	n.d.	3-20
Parathormone (PTH) (pg/mL)	n.d.	49.0	n.d.	n.d.	18-87
Antithyroglobulin Ab (chemiluminescence)	<20	n.d.	n.d.	n.d.	<40
Blood cortisol (µg/dL)	n.d.	n.d.	15.3	n.d.	5-25
Dehydroepiandrosterone sulfate (DHEAS) (µg/dL)	n.d.	n.d.	159	n.d.	35-430
Adrenocorticotropic Hormone (ACTH) (pg/mL)	n.d.	n.d.	12.1	n.d.	9-52
Aldosterone (ng/dL)	n.d.	n.d.	11.2	n.d.	2.4-22.0
Renine (µU/mL)	n.d.	n.d.	9.1	n.d.	4.4-46.0
Urine hormone metabolites					
Vanilmandelic acid (mg/24 hours)	n.d.	n.d.	n.d.	5.9	<7.5
Homovanilic acid (mg/24 hours)	n.d.	n.d.	n.d.	6.6	<7.5
Epinephrine (µg/24 hours)	n.d.	n.d.	n.d.	10.6	<14.9
Nor-Epinephrine (µg/24 hours)	n.d.	n.d.	n.d.	38.5	<66.07
Dopamine (µg/24 hours)	n.d.	n.d.	n.d.	366	<591.80

Table 3. Immunological situation of the patient.

Blood immunology	At 31 years of age, before surgery	Normal values
Anti-endomysium Ab (immunofluorescence)	Negative	Negative
Anti-transglutaminase Ab (UR/ml)	<2	<20
Anti Nuclear Antibody (ANA)	Negative	Negative (≤1 : 40)
Extractable Nuclear Antigen (ENA) screen	Negative	Negative
Islet Cell Antibodies (ICA)	Negative	Negative (≤1 : 10)
Glutamic Acid Decarboxylase (GAD) antibody	5 UI/mL	Positive ≥10
Anti-DNA Ab	Negative	Negative (≤1 : 10)
Circulating immunocomplexes		
Anti C1q antibody	2 µgEq/mL (negative)	Positive >4
C3 complement component	8 µgEq/mL (negative)	Positive >20
Aquaporin 4 (NMO IgG) Ab	Negative	Negative

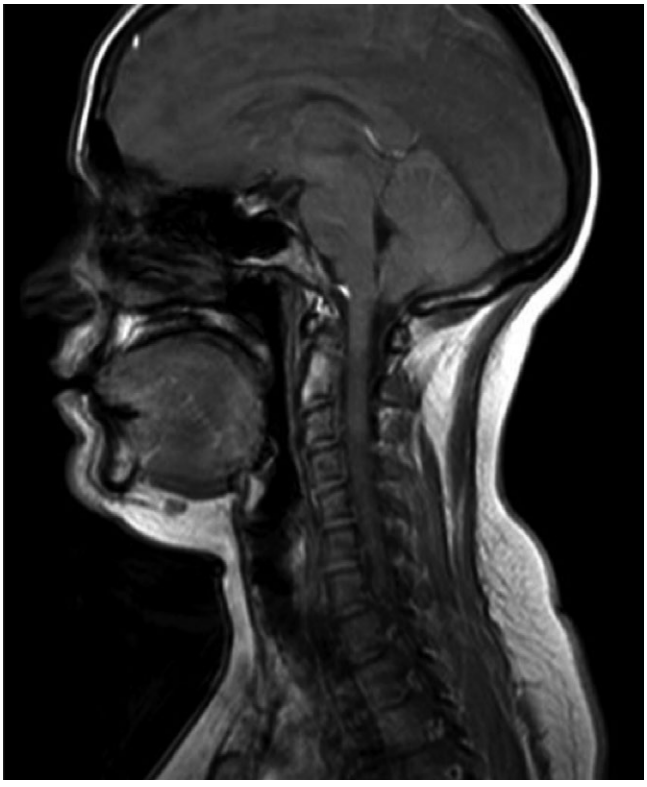

Figure 2. Sagittal MRI of the posterior fossa and upper cervical spine at 34 years, after shunting. Tonsil tips lowered no more than 5 mm from the plane of foramen magnum.

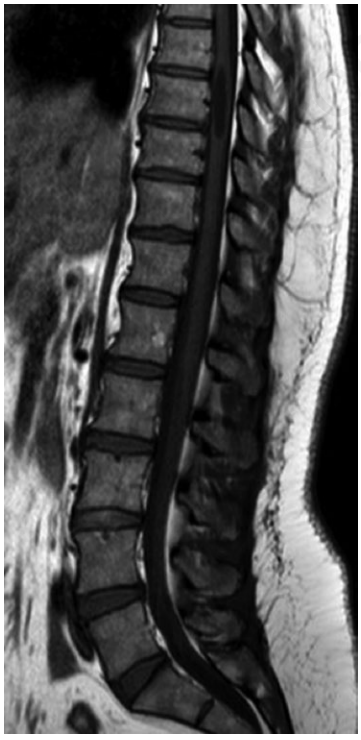

Figure 3. Sagittal MRI of dorso-lumbar spine. Presence of a cavity filled with a cerebro-spinal like liquid.

a foramen magnum abnormality is always present and this condition could act as valvular obstruction to the upward flow of the CSF during coughing, straining, posture changing and muscular activity.[14] If the hindbrain lesion acting as valve does not permit the prevention of the normal dissipation of waves associated to these physiological activities and transmitted from the subarachnoideal spinal space, the pressure waves might inverted and spread CSF in the chord along the perivascular Virchow-Robin spaces, causing syrinx. This mechanism is also reported in the patient subgroup, who do not exhibit frank tonsillar ectopia, but a *benign tonsillar ectopia*[8] with associated syrinx. This condition is considered as CMI because it presents positive results on syringomyelia after the posterior fossa decompression.[8]

On the basis of the pre-surgical symptomatology (mainly papilledema and headache), this condition could have been present in our patient before shunting.

In some cases, syrinx of CMI may be an acquired condition, consequent to spinal peritoneal shunt placement, with increased spinal CSF absorption due to the high intracerebral-spinal pressure gradient which could induce the tonsillar descent and, due to Ball and Dayan[13] mechanism, the syrinx formation.[7,15]

Scoliosis may be associated to syringomyelia; in 4% of symptomless patients who undergo surgery for scoliosis, syringomyelia

Table 4. Cardiological results in the patient before surgery.

Parameter	Recorded value
Arterial Pressure (AP) (Riva Rocci)	90/60 mmHg
Heart beat frequency	54/min
Respiration frequency (breaths)	12/min
Body temperature	36.6°C
ECG	normal

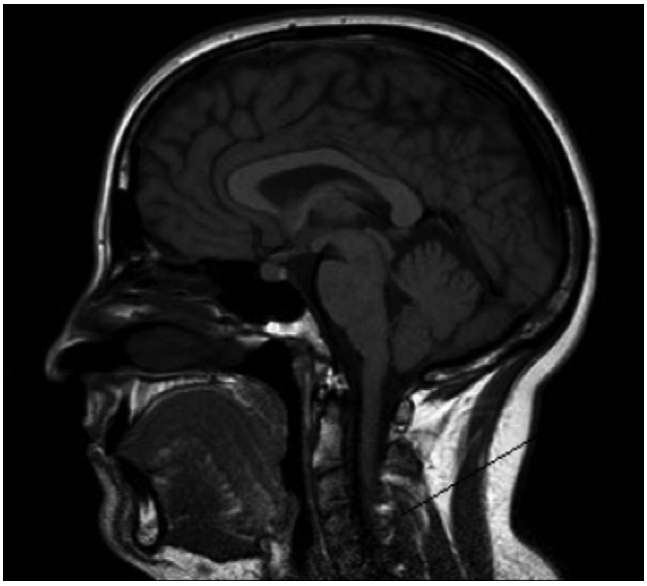

Figure 4. Sagittal cranial MRI at 34 years 6 months, confirming previous tonsil tips position.

Table 5. A: Motor Evoked Potentials following transcranial magnetic stimulation showing raised latency in left inferior limb due to delay of motor central conduction to left inferior limbs. B: Somato-sensorial evoked potentials following median nerve stimulation at wrist: values within normal range. C: Somato-Sensorial Evoked Potentials after stimulation of tibialis nervus at ankle; cortical response: bilateral delay of latency of reference peak P40 (left>right).

A Musculus	Cortical stimulation(msec.)	Radicular stimulation(msec.)	TCCM
Opponens pollicis dexter	19 (n.v. 19.5±1.5)	12.4	6.60
Opponens pollicis laevus	18.5 (n.v. 18.5±1.5)	12.4	6.10
Tibialis anterior dexter	28.5 (n.v. 29±1.5)	12.9	15.6
Tibialis anterior laevus	31.1 (n.v. 28.5±1.5)	13.5	17.6
B			
Cervical response		Right	Left
Latency of the reference peak N13	msec (n.v. <16.3)	13.7	13
Cortical response latency of the reference peak N20	msec. (n.v. <22.1)	20.2	19.5
Central conduction time	msec. (n.v. <6.8)	6.50	6.50
C			
Cortical response latency of the reference peak P40	msec. (n.v. <40)	44.8	46.8

was present[16,17] as expression of a common malformative pathogenetic mechanism.[18] In some cases scoliosis is associated to syringomyelia and to CMI.[1,2]

In our patient, spinal abnormalities (reduced lordosis, protrusion of lumbar disks) may have a relationship with CMI abnormality and syringomyelia.

Tubbs *et al*.[8] reported a particular condition, connected to CMI malformation and observed in 8% of cases of this syndrome: the occurrence of thin arachnoid membrane occluding the Magendie foramen, not demonstrated at MRI, but diagnosed at surgery. This condition caused CSF flow defect and CMI malformation and was resolved after bone cerebellar fossa decompression and membrane ablation[8]. In our patient this condition may be excluded, owing to the positive functionality of shunt,[7] but it poses the issue of the association of facial abnormalities with cerebellar and posterior cranial fossa malformations.[19,20]

Couly and Aicardi[19] reported the frequent association of lateral facial abnormalities, maxillo-mandibular disostoses present in Goldenhar/OAVS syndrome, with malformations of brain stem, cerebellum, meninges, posterior cranial fossa, and attributed these abnormalities to NCC abnormal migration-proliferation and integration with the mesoderm.[20,21]

In our patient, mild hemifacial microsomia, ear abnormalities,[22] skin blind fistulas, homolateral to prevalent papilledema, to lateral venous sinus cerebral hypoplasia, and to underdeveloped cerebral left ventricle are present on left side and are associated to brain stem, ocular and spinal abnormalities. All these malformations are mild, but the symptomatology is clinically relevant. These malformations depose for a complex malformation syndrome reminiscent of OAVS,[23-28] associated to CMI malformation, syringomyelia and papilledema. This association, here reported first to our knowledge, should be a typical neurocristopathy due to abnormal proliferation, migration or integration of NCC with tissues[21] and to their regulatory role on the mesoderm development.[19,21-23,25-28] On this basis, in our case, CMI abnormality may be congenital, associated to papilledema and syringomyelia with spinal abnormalities, and connected to OAVS as extension of this spectrum. This case underlines the relevance of the development of studies connected to clinical signs,[29] although mild, for taking the diagnosis, and the need of early surgical therapy in the presence of papilledema to avoid the blindness. After five years from surgery, the patient is well, without papilledema and with only a mild restriction of visual fields. Further studies are necessary to confirm this unitary pathogenetic hypotheses of CMI syndrome, syringomyelia, papilledema, and OAVS.

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