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A unique case of progressive hemifacial microsomia or Parry-Romberg syndrome associated with limb and brain anomalies with normal neurological findings: A review of the literature

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ABSTRACT

In this report, we describe an unusual case of progressive hemifacial atrophy or Parry-Romberg syndrome in a 10-year-old girl with progressive hemifacial microsomia and limb anomalies who had brain magnetic resonance imaging (MRI) findings of white matter hyper-intensities. Patients typically present with neurological manifestations such as epilepsy, facial pain, and migraines and ophthalmological symptoms in conjunction with white matter lesions. The patient demonstrated normal cognition and psychomotor development despite the presence of white matter lesions in her frontal lobe that is commonly associated with neurological symptoms. This report brings attention to the complicated relationship between facial, limb and brain imaging findings in Parry-Romberg syndrome and differentiates it from hemifacial microsomia syndrome.

1. Introduction

Parry-Romberg syndrome (PRS) is a rare neurocutaneous disorder that was first described by Caleb Parry in 1825 and further studied by Moritz Romberg in 1846 (Xu et al., 2013). PRS is characterized by progressive hemifacial atrophy (PHFA) that often coexists with en coup de sabre, a specific form of linear scleroderma found on the forehead and frontoparietal scalp (Maletic et al., 2010; El-Kehdy et al., 2012). Neurological symptoms that PRS patients most often experience are seizures, trigeminal neuralgia, and migraines (Maletic et al., 2010; El-Kehdy et al., 2012; Stone, 2003; Mazzeo et al., 1995). Some affected patients also present with ophthalmological manifestations such as enophthalmos, uveitis, and heterochromia (Maletic et al., 2010; Stone, 2003). The etiology of PRS is still not fully understood, although some have postulated that it may have an autoimmune basis (El-Kehdy et al., 2012; Stone, 2006). Other theories suggest sympathetic cervical ganglion dysfunction or abnormal embryogenesis in the etiology of PRS (Wong et al., 2015). PRS usually manifests between 5 and 15 years of age and has been shown to affect females more frequently than males (Xu et al., 2013). Overall, PRS is a self-limiting disease that is not generally fatal (El-Kehdy et al., 2012; Mazzeo et al., 1995; Stone, 2006).

We describe the severe cutaneous and skeletal muscle manifestations in a 10-year-old female patient with Parry-Romberg syndrome. The patient described in this case report had abnormal brain magnetic resonance imaging (MRI) that showed white matter lesions of the frontal lobe. Remarkably, she did not exhibit significant PRS neurological manifestations impairing her cognitive or psychomotor abilities that are typically associated with this syndrome.

2. Case report

We report a 10-year-old female patient of Mexican descent who was diagnosed with Parry-Romberg syndrome at 3-years-old. She was born vaginally to a healthy 23-year-old mother and 30-year-old father. The pregnancy was complicated by decreased fetal movements and hyperglycemia. Her birth head circumference, length and weight was not available but was reported as normal. There was no family history of scleroderma or Parry-Romberg syndrome.

At age 3 years, the patient was observed to have regions of scleroderma, involving hyperpigmentation and atrophy, on her trunk and

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limbs. She demonstrated facial asymmetry, which progressed until she developed significant right hemifacial atrophy and a deep indentation with a bluish-tinged vascular malformation along the midline of her forehead (Fig. 1) and gradual involvement of a large region on the left side of her neck (Fig. 2A) and her right ear which was significantly smaller. She also developed involvement of the skin over her left lower limb and by age 6 years it was underdeveloped compared to the right (Fig. 2B).

Additionally, multiple neurological examinations of the patient since age 3 years were reported as unremarkable with no focal abnormalities. She was consistently found to be alert, oriented, and to have a full range of eye movements and well-functioning cranial nerves. She was consistently observed to have a normal gait with normal muscle strength, tone, range of motion, and reflexes. She had a negative history of seizures, and at age 8 years an electroencephalogram study reported no areas of focal slowing or epileptiform abnormalities. She did, however, experience infrequent, mild facial pain, and recurrent headaches which were treated symptomatically, the latter being attributed to a family history of headaches and less likely related to PRS.

A brain MRI scan, performed at 3 years of age, revealed abnormal white matter signals in the right frontal subcortical region. The findings showed a mild peritrigonal white matter signal abnormality that was asymmetrically prominent on the right and a mild asymmetric periventricular white matter signal abnormality adjacent to the right lateral ventricle. There was, however, predominant sparing of the subcortical U fibers. MRI findings also revealed right sphenoid sinus disease and mild bilateral mastoid fluid which later resolved. Further follow-up brain MRI scans at age 4 years, 5 years, 6 years, 7 years, and 8 years (Fig. 3) revealed stable T2 white matter hyper-intensities and no significant interval changes compared to previous MRI reports.

At age 4 years, the patient had a skin biopsy of sun-exposed non-lesional skin that was evaluated by direct immunofluorescence studies which showed significant deposits of IgM and C5b-9 along the dermal-epidermal junction and vascular deposits of IgM and C5b-9 indicative of an autoimmune etiology. The patient's blood studies were negative for anti-endothelial cell antibodies. She was treated with steroid creams which were reported to help; however methylprednisolone injections were reported to be ineffective.

In general, the patient's physical appearance and neurological status have been stable upon evaluation over the years, despite a diagnosis of PRS at an early age. Her most recent measurements at 9 years 8 months were: head circumference 53.5 cm height 140.2 cm, weight 36.7 kg. (Z scores 0.15, 0.56 and 0.71 respectively). Recently SNP microarray testing in a blood sample did not reveal any chromosomal abnormalities.

3. Discussion

The 10-year-old female in the present case report has had a long-term brain MRI and clinical follow-up starting from the first diagnosis at age 3 years. She had severe facial features including progressive hemifacial microsomia (PHFM) and en Coup de Sabre with limb involvement. The patient's brain MRI findings showed white matter lesions in the right frontal subcortical region that remained unchanged from the ages of 3–8 years and were not associated with neurological impairment. She had normal psychomotor development, as evidenced by her normal developmental milestones, gait, and lack of obvious muscle weakness. She was able to attend school at her grade level, had normal social interactions, and did well on school evaluations with no special education services requirements.

We reviewed the literature for similar cases with limb, hemifacial microsomia, and brain MRI white matter hyperintensities (WMH) as seen in our patient with normal cognition and neurological findings. Zulian et al. reported only eight cases with isolated PHFM and six with both PHFM with head and limb involvement among 113 patients with juvenile localized scleroderma (Zulian et al., 2006). Detailed information on these subjects, however, was not available in this report. We found a few isolated reports of hemifacial atrophy and limb anomalies (Table 1), including a case report of a 48-year-old female with hemifacial atrophy but normal brain MRI (Aydın et al., 2015) and an 11-year-old boy with severe scleroderma of left side of the body and intellectual deficit with an abnormal brain MRI (Grosso et al., 2003). In a report of 19 cases of PHFM, several had morphea or linear scleroderma of the trunk and/or extremities; however, details were not available and brain anomalies were not investigated (Blaszczyk et al., 2003).

The literature was also reviewed for patients with PRS, without associated limb involvement, with brain white matter involvement. A study of a cohort of 10 patients with PRS revealed that half of the patients had abnormal MRI findings, most frequently in patients who also exhibited neurological symptoms (Moko et al., 2003). These abnormal MRI findings were most frequently WMH and cerebral hemiatrophy,

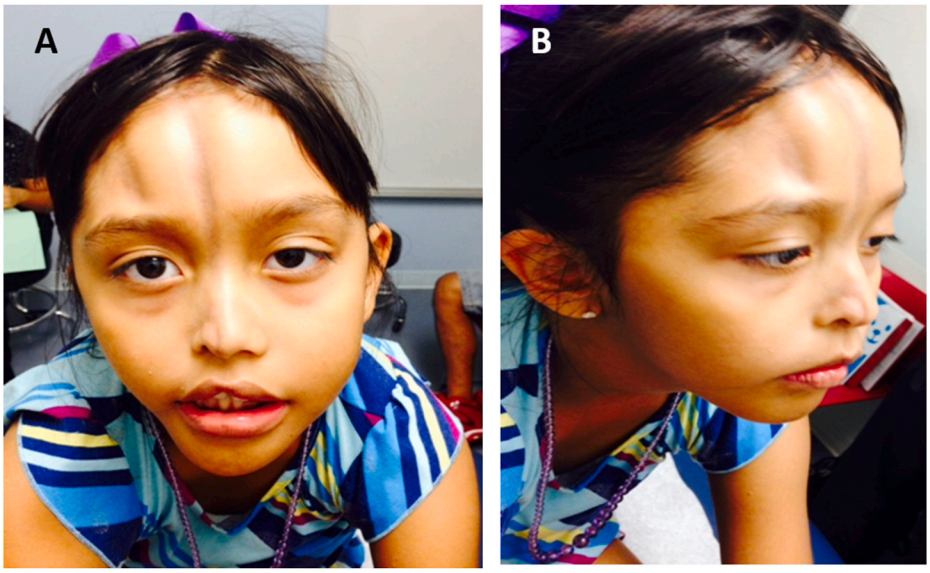

Fig. 1. Craniofacial Features associated with Parry Romberg syndrome. A. Frontal view of the face reveals midline indentations of the forehead extending into the nose and right sided hemifacial atrophy.
B. Side view of the face showing the bluish-tinged indentation of the forehead.

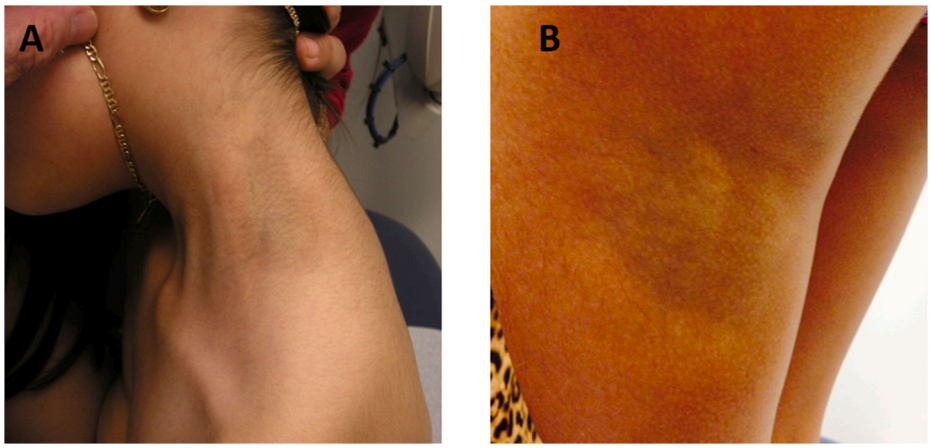

Fig. 2. Areas of subcutaneous and muscular atrophy of the neck and thigh. A. Left side view of the neck shows a patch of subcutaneous atrophy B. An area of subcutaneous and muscular atrophy of the left thigh.

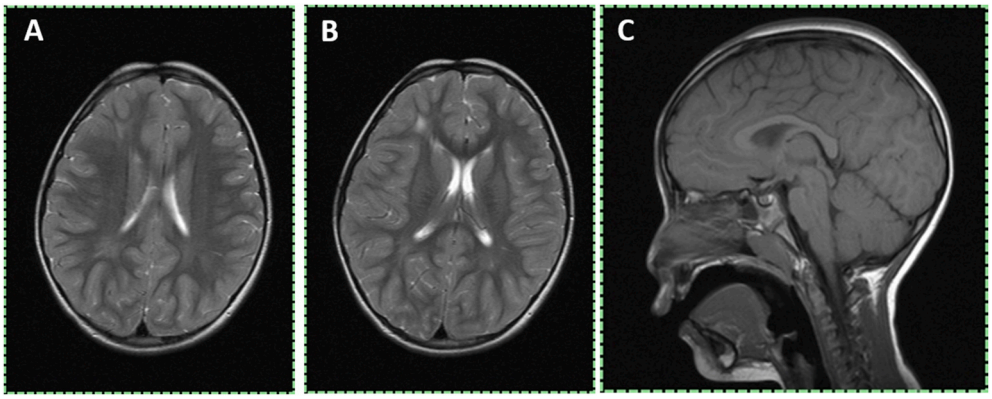

Fig. 3. Brain magnetic resonance imaging (MRI) findings in the patient at age 4 years: T2 axial (left, middle) and T1 sagittal (right) reveals white matter hyperintensities of the peritrigonal and periventricular region adjacent to the right lateral ventricle.

Table 1
Comparison of Clinical and Neuro-Imaging findings of the present case with patients reported in detail in the literature.

	Age (Y)	Sex	Face		Limbs		Brain MRI changes	Psychomotor development	Progression	Other findings
			R	L	R	L				
Present case	**10**	**F**	+	-	-	+	White matter lesions (Right frontal subcortex)	Normal	+	-
Aydın et al. (2015)	**48**	**F**	-	+	-	+	Asymmetric fatty loss of scalp and galeal subcutaneous fatty tissue (Left frontal) No cortex white matter anomaly	Normal	-	-
Grosso et al. (2003)	**11**	**M**	-	-	-	+	Left cerebral hemisphere atrophy (Sylvian fissure)	Intellectual deficit	-	Recurrent complex partial seizures
Vix et al. (2015)	**55**	**M**	+	-	-	-	WMH of the right cerebral hemisphere	Normal	-	Trigeminal neuralgia Right-sided deafness
Vix et al. (2015)	**44**	**F**	-	+			WMH left frontal lobe	Normal		
Klimiec and Klimkowicz-Mrowiec (2016)	**23**	**F**	+	-	-	-	Right temporal lobe atrophy	Mild cognitive Impairment	+	-
Okumura et al. (2006)	**5.4**	**M**	-	+	-	-	White matter lesions (Left cerebral hemisphere)	Normal	+	-

M = male, F = female, R = Right side, L = left side, WMH = white matter hyperintensities.

interestingly most frequently on the ipsilateral side of the HFA (Wong et al., 2015; Moko et al., 2003).

PRS patients may present with neurological complications including, but not limited to, seizures, headaches, and neuropsychological symptoms (Vix et al., 2015). In one study on 32 patients aged 3–17 years with PRS, 28% had additional neurologic symptoms, most common being seizures (Vix et al., 2015\). A detailed report of a 55-year-old male patient with HFA indicated he had extended areas of T2-FLAIR WMH involving posterior occipital and part of the corpus callosum, the caudate nucleus, and the anterior limb of the internal capsule of the right hemisphere but without significant cognitive impairment (Vix et al., 2015). Long-term follow-up of a 9-year-old male PRS patient revealed

stable neurological and MRI findings despite the progression of his facial atrophy (Klimiec and Klimkowicz-Mrowiec, 2016). Observation of a male from age 22–65 months revealed normal psychomotor and neurological development despite white matter lesions involving the entire left cerebral hemisphere (Okumura et al., 2006).

The differential diagnosis of progressive hemifacial microsomia includes hemifacial microsomia (HFM) syndrome, a sporadically occurring disorder of unknown etiology. It is associated with congenital malformations of the first and second branchial arches resulting in facial asymmetry with unilateral hypoplasia of maxilla, mandibular, zygoma, temporal bones, and surrounding soft tissue. HFM and Goldenhar syndrome are considered variants under the same clinical continuum of disorders termed the oculo-auriculo-vertebral spectrum. Goldenhar syndrome encompasses HFM phenotypes along with epibulbar dermoid and vertebral anomalies. Cranial nerve abnormalities and function deficits occur in some individuals; however, the marked atrophy of the limbs and brain white matter changes are not seen in HFM (Strömland et al., 2007). Berardinelli-Seip congenital generalized lipodystrophy is suspected in individuals with lipoatrophy affecting the trunk, limbs, and face. In some individuals, the face may be normal at birth with lipoatrophy of the face and body becoming apparent during the first months of life. Skeletal muscle hypertrophy is also present giving the individual an athletic appearance. The disorder is associated with elevated serum concentration of triglycerides and insulin resistance.

Direct immunofluorescence studies of our patient's sun-exposed non-lesional skin showed significant deposits of IgM and C5b-9 along the dermal-epidermal junction and vascular deposits of IgM and C5b-9 indicative of an autoimmune etiology. Additionally PRS are typically sporadic providing evidence against a genetic association of this condition. Only two cases were reported in biological first cousins (Anderson et al., 2005). Nevertheless future trio genome sequencing is being explored for our unique patient. A case of a woman who was misdiagnosed as multiple sclerosis indicate that the brain lesions in PRS are located in the same region as in multiple sclerosis (Long et al., 2020). The authors thus hypothesized that PRS may be an autoimmune inflammatory process. The variability in MRI findings and clinical features of PRS may be a reflection of the multiple pathogenetic pathways involved in different patients (Long et al., 2020).

Currently, there is no cure or any proven treatment available for PRS (Mazzeo et al., 1995; Stone, 2006), although immunosuppressant drugs have been shown to be beneficial in some cases, thus supporting the theory that PRS may be an autoimmune disorder (El-Kehdy et al., 2012; Stone, 2006). In the case of our patient, methylprednisolone injections were reported as ineffective. In a clinical study, it was found that collagen-polyvinylpyrrolidone could be a potential new treatment for PRS since it works well in alleviating hemifacial atrophy and inflammation (Hernández-Vega et al., 2013). Restorative plastic surgery using fat or silicone implants, flap grafts, or bone implants is often beneficial for PRS patients (Mazzeo et al., 1995; Stone, 2006). At the age of 9 years, our patient underwent fat grafting, without issues, and her facial deformities were much improved. Although surgeries may prevent further atrophy of the face, it is usually recommended after the disease has run its course (El-Kehdy et al., 2012).

In conclusion, our present understanding of the etiology of this rare disorder is limited. There has been little study of the significance of white matter lesions, how these lesions arise in the brain, and how they are related to the other PRS features. The comparison of other cases with our patient demonstrates that the presentation of neurological manifestations and cerebral white matter atrophy in PRS patients is quite variable. Thus, the findings in our unique patient with PHFM, limb atrophy, and brain findings present an important opportunity to further understand the enigmatic disease that is PRS.

CRediT authorship contribution statement

Anandita Pattnaik: Data curation, Writing – original draft. **Alexandra Lim:** Writing – review & editing. **Sara Sabeti:** Writing – review & editing. **Ashley Kwon:** Writing – review & editing. **Ira Lott:** Writing – review & editing, Validation. **Virginia Kimonis:** Conceptualization, Methodology, Resources, Writing – review & editing, Supervision, Validation, and, Supervision.

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