Parry-Romberg syndrome in Kuwait

Neurological manifestations in 2 children

***Mohamed Zakkiriah**, MD, **Maryam KH. Al Khalaf**, MD, **Muna A. Al Mutairi**, MD, **Sarah Al Enezi,** MD.*

ABSTRACT

متلازمة باري رومبرج هو اضطراب نادر مع ضمور نصفي تدريجي مجهول السبب. نستعرض في هذا التقرير حالتين لضمور نصفي تدريجي مع أعراض عصبية مختلفة من الكويت. الحالة الأولى كانت لذكر يبلغ من العمر 14 عامًا عرض علينا في البداية بنوبات متكررة تشبه السكتة الدماغية تليها نوبات بؤرية وضمور نصفي. أظهر التصوير بالرنين المغناطيسي تغيرات مهمة في المادة البيضاء وضمور دماغي شقي. الحالة الثانية كانت لطفلة تبلغ من العمر 7 سنوات قدمت لها نوبات جزئية معقدة وضمور نصف الوجه، وأظهر مسحها للرنين المغناطيسي تغيرات طفيفة في الدم في الفص الدماغي الصدغي. تم التحكم بشكل جيد في نشاط المرض للمرضى من خلال العلاج المثبط للمناعة ومضادات الاختلاج. يجب اعتبار متلازمة باري رومبرج في أي طفل يعاني من أعراض عصبية غير مفسرة.

Parry-Romberg syndrome is a rare disorder with progressive hemifacial atrophy of unknown etiology. We reported 2 cases of progressive hemifacial atrophy with different neurological manifestations from Kuwait. The first case was a 14-year-old boy who initially presented with recurrent transient stroke-like episodes followed by focal seizures and hemifacial atrophy. Magnetic resonance imaging showed significant white matter changes and cerebral hemiatrophy. The second case was a 7-year-old girl who presented with complex partial seizures and hemifacial atrophy, her magnetic resonance imaging scan showed minimal changes in the hemiatrophy of the temporal cerebral lobe. Both patients' disease activity was well controlled with immunosuppressive therapy and anticonvulsants. Parry-Romberg syndrome should be considered in any child with unexplained neurological symptoms.

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From the Department of Neurology (Zakkiriah, Al Enezi), and from the Department of Rheumatology (Al Khalaf, Al Mutairi), Al Adan Hospital, Ministry of Health, Hadiya, Kuwait.

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Address correspondence and reprint request to: Dr. Maryam Kh. Al Khalaf, Department of Rheumatology, Al Adan Hospital, Ministry of Health, Hadiya, Kuwait. E-mail: maryamkhalaf@hotmail.co.uk
ORCID ID: https://orcid.org/0000-0003-2029-4790

Parry-Romberg syndrome is an uncommon acquired neurocutaneous disorder that is characterized by progressive unilateral atrophy of the face. The trunk and limb involvement is rare.[1,2] Parry (1825) and Romberg (1846) described the syndrome initially and subsequently in 1871; Eulenberg coined the term progressive facial hemiatrophy.[3] It usually manifests in late childhood or adolescent period of life and slowly progresses over up to 20 years and then stabilizes.[1] The etiology is unknown and possible etiologies includes viral, genetic, autoimmunity and altered autonomic imbalance that could lead to facial atrophy and cerebral atrophy.[4]

The disease is more common in females and approximate incidence of the disease per year is 3/100000. The neurological manifestation can occur quite early in the natural history and the mean age at onset of the neurological symptoms was 20.9 (1.5-73 years).[5] Neurological symptoms may occur earlier than the skin lesions and it is not correlated with facial atrophy.[6] The hemifacial atrophy can be accompanied by focal neurological deficit such as hemiplegic migraine[7] and rarely ischemic stroke.[8]

Parry-Romberg syndrome mainly affects one side of the face including skin, subcutaneous tissue, muscle, cartilage, and bone leading to the hemifacial atrophy. Sometimes hyperpigmentation or depigmentation, alopecia also noted.[3] Current evidence suggests that a

1-2 year course of methotrexate is the most effective treatment for inducing prolonged remission.

Case Report. *Case 1: Patient information.* A 14-year-old Kuwaiti boy who presented at the age of 10 years with recurrent, transient stroke-like attacks. He felt numbness and heaviness on the right side and difficulty using his right hand for 15-20 minutes. There was no loss of consciousness or speech disturbance, although he experienced mild headache in the left frontotemporal area for 5 minutes. After 3 months, the patient started to have right focal seizures without loss of consciousness lasting approximately 3-4 minutes. The seizure frequency was 2-3 episodes per month.

Clinical findings. Neurological examination was normal and there was no focal neurological deficit. Two years later, he developed darkening of the left side of his face that progressed to hemiatrophy with hardening of the skin of the forehead, cheek and nose, as well as alopecia on the left side of scalp (**Figure 1**).

Diagnostic assessment. His complete hemogram, liver function test and renal function test revealed normal values. Erythrocyte sedimentation rate and c-reactive protein (CRP) were normal. Also the C3, C4 normal. ANA, P-ANCA, C-ANCA, anti- phospholipid AB, anti- cardiolipin AB and Von willebrand factor antigen were negative.

Serum angiotensin converting enzyme (ACE) level and serum homocysteine level normal. Lactate, ammonia, urine organic acid screen, and blood amino acid revealed no significant abnormality. Hyper coagulation screen normal. Gene test for mitochondrial encephalopathy, lactic acidosis, and stroke-like, myoclonic epilepsy with ragged red fibers were negative. Cerebrospinal fluid (CSF) values are normal except mild increase in the CSF protein 48 mg/dL (normal value 15-45mg/dL). Immunoglobulin oligoclonal bands absent.

An electroencephalogram (EEG) showed focal cerebral dysfunction in the left anterior quadrant and epileptiform abnormalities in the left parasagittal area.

Magnetic resonance imaging of the brain scan revealed increased signal intensities in the left hemisphere, mainly in the frontal lobe, with multiple areas of microhemorrhages and calcifications (**Figure 3**). Magnetic Resonance Angiography and magnetic resonance venography were normal.

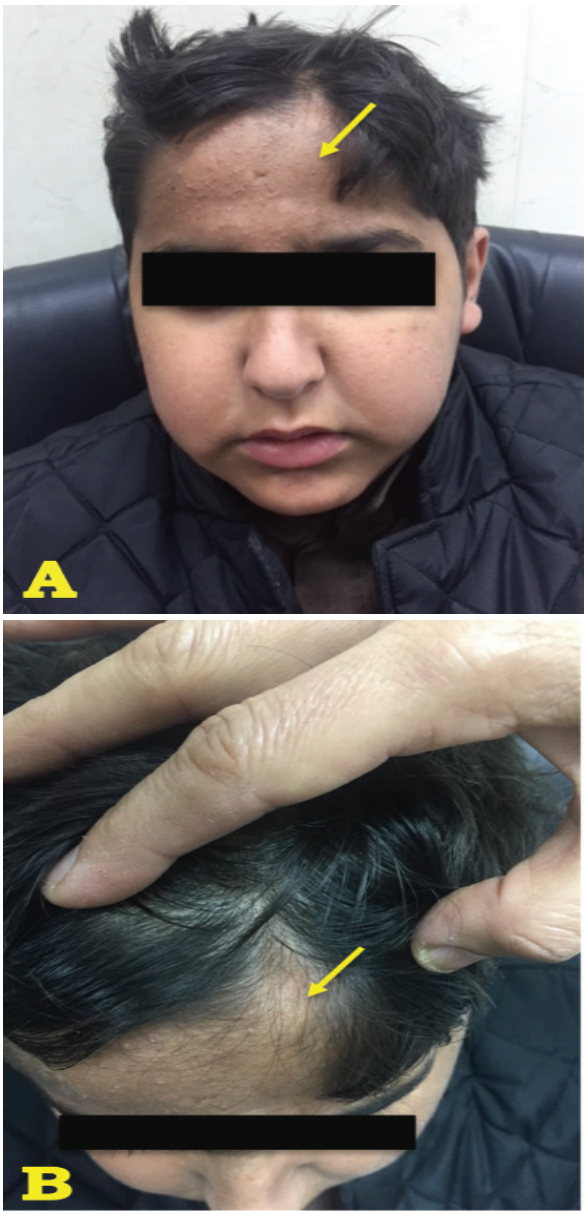

Figure 1 - Area of depression that involved the region near his hairline (**A**). With depression of his left nostril with some alopecia involving the left frontal scalp (**B**).

Therapeutic intervention. His seizures were well controlled with oxcarbazepine. His disease activity was well controlled with a course of prednisolone for one year then phased out. Methotrexate also started together and he is taking it until now.

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Table 1 - Timeline of a 14 year old boy normal birth history and development. He started having symptoms from the age of 10 years. No family history of any neurological illness.

Date	Presentation	Diagnostic tests	Intervention
10 January 2015	Right hand stroke Left side headache	CT brain: hypo dense lesion in left frontal and basal ganglia	
17 January 2015		MRI brain: extensive white matter changes, micro hemorrhages and gliosis in the left side. MRA, MRV normal. ESR, CRP, LFT and RFT normal. CSF values are normal except mild increase in the CSF protein 48 mg/dL (normal value 15-45mg/dL). IgG oligoclonal bands absent.	
25 January 2015		Blood amino acid and urine organic acid normal. Lactate, ammonia normal.	
15 February 2015		C3, C4 normal. ANA, P-ANCA, C-ANCA, anti- phospholipid AB, anti- cardiolipin AB and Von willebrand factor antigen were negative. Serum ACE level and serum homocysteine level normal. Hyper coagulation screen normal.	
15 March 2015		Gene test for MELAS, MERFF negative.	
21 April 2015		MR spectroscopy normal.	
30 April 2015	Right focal seizures 3 episodes in one week	EEG showed focal cerebral dysfunction in the left anterior quadrant and epileptiform abnormalities in the left parasagittal area.	Oxcarbazepine 20mg/kg/day started gradually
15 July 2015	Right focal seizures again 4 attacks. Symptoms free until February 2017		Oxcarbazepine increased to 30mg/kg/day
20 February 2017	Dimple on his left forehead, mild alopecia and darkening of the left side of the face.		
15 March 2017		MRI showed more white matter changes and obvious cerebral hemiatrophy. Shrinkage of left orbit and maxillary sinus enlargement.	Prednisolone 2mg/kg/day for 2 weeks then tapered to one mg/kg/day for one year and Phased out. Methotrexate 0.5mg/kg/wk started
June 2017- until now		Every 3 months follow-up with CBC, LFT, RFT all normal.	
February 2019	Static course no progression of hemi facial atrophy.	Repeat MRI no new changes. EEG epileptiform abnormalities in left fronto central area	Methotrexate 0.5mg/kg/wk still continuing

CT - computerized tomography, MRI - magnetic resonance imaging, MRA - magnetic resonance angiography, MRV - magnetic resonance venography, ESR - erythrocyte sedimentation rate, CRP, - C reactive protein, LFT - liver function test, RFT - renal function test, CSF - cerebrospinal fluid, C3, & C4 - complement level 3 & 4, ANA - antinuclear antibodies, P-ANCA - Perinuclear anti-neutrophil cytoplasmic antibodies, C-ANCA - cytoplasmic anti-neutrophil cytoplasmic antibodies, ACE - angiotensin converting enzyme, MELAS - miotochondrial encephalo myopathy, lactic acidosis and stroke, MERFF - myoclonic epilepsy with ragged red fibers, MR - magnetic resonance, EEG - slectroencephalogram, CBC - complete blood count

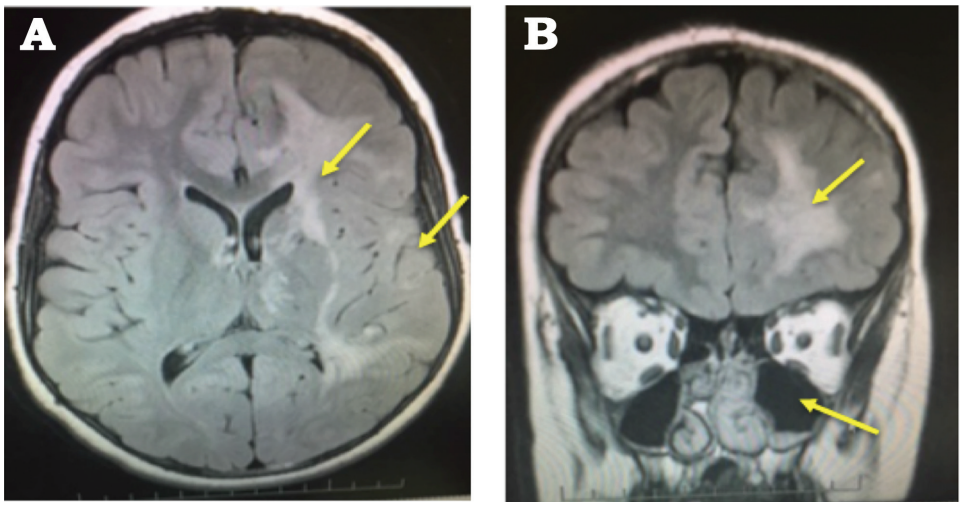

Figure 2 - A) Signal hyperintensities of the left white matter and cerebral atrophy. B) Coronal section shows shrinkage of the left orbit and maxillary sinus enlargement.

Follow-up and outcomes. He is seizure free for more than 3 years and follow-up MRI showed static course and no progression of hemi facial atrophy.

Case 2: Patient information. A 7-year-old Kuwaiti girl started to have right focal seizures with secondary generalization at the age of 5 years. Her seizures were initially controlled with an anticonvulsant for one year and then she started to have frequent seizures (2-3 episodes per week). Her birth history and development was normal. There was family history of epilepsy with her mother and her school performance was average.

Clinical findings. She was found to have hyperpigmentation and hardening of the skin in addition to alopecia over the left side of her face. With time, hemiatrophy of the face started to become more obvious (**Figure 3**). Her neurological examination was normal and there was no focal neurological deficit.

Diagnostic assessment. complete hemogram, liver function test and renal function test revealed normal values. Erythrocyte sedimentation rate and CRP were normal, also C3, C4 were normal. ANA, P-ANCA, C-ANCA were negative. Electroencephalogram showed spike wave activity over the left centro temporal area. The computed tomography brain scan showed left temporal lobe calcification. The MRI showed hemiatrophy of the left cerebral hemisphere with signal intensity in the left temporal lobe (**Figure 4**).

Therapeutic intervention. Her seizure activity initially was controlled with sodium valproate for one year and then she started to have frequent seizures which were controlled with oxcarbazepine and levetiracetam. She was also treated with prednisolone for one year and phased out and methotrexate was started along with prednisolone and still going on.

Follow-up and outcomes. Her seizures were well controlled with anticonvulsant and disease activities stable confirmed with follow-up MRI. Periodic complete blood count and liver functions test were normal.

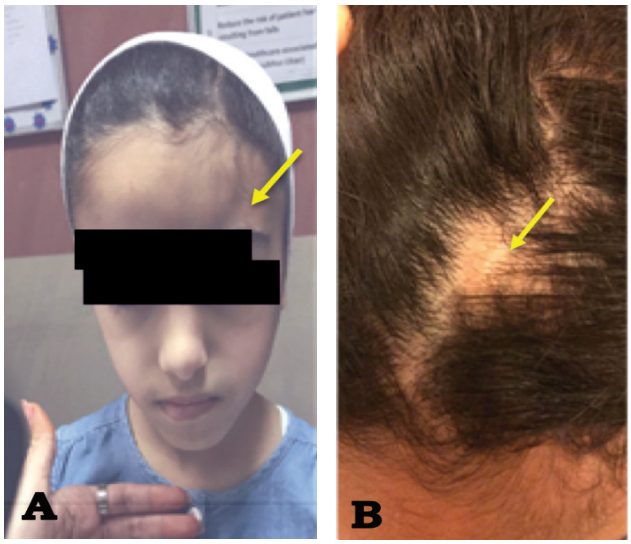

Figure 3 - A) left-sided atrophy with hyperpigmentation, b) area of alopecia on frontal scalp

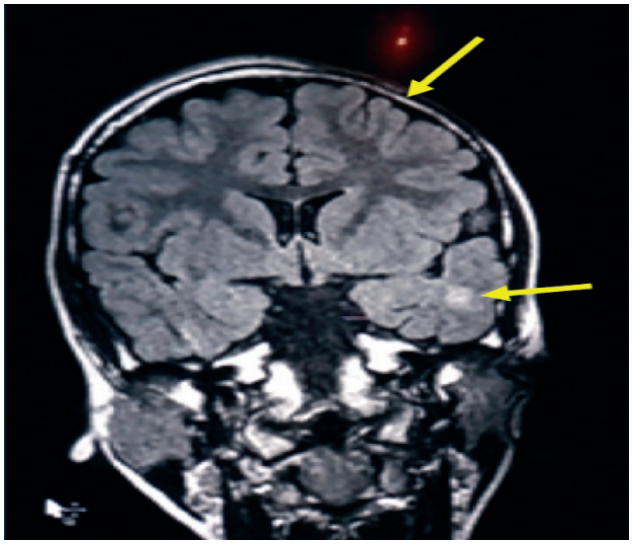

Figure 4 - Hemiatrophy of the left side with abnormal signal in the subcortical left temporal region and left periventricular area.

Discussion. As per the Stone et al[9] global survey of 205 patients on Parry-Romberg syndrome only 11% of the patients had epilepsy and median age of on set was 10 years. Both of our patients started symptoms at in the first decade of life and also had seizures.

Case 1 had fewer seizures but more MRI changes than case 2. Case 2 had more skin changes and seizures but fewer MRI changes than case 1. Patient 1 had mild enophthalmos and sinus enlargement on the left side, which has been reported in Parry-Romberg syndrome.

Though few cases of Parry-Romberg syndrome had been reported from the Middle East region[9] most of them were adult except as case from Egypt 11 year old boy and most of the cases reported with hemifacial atrophy none of the cases were reported with neurological manifestation like epilepsy, stroke like episode and typical MRI brain changes.[5]

The study carried out by Vix J et al,[5] showed MRI brain abnormalities were noted in 75% of patients. Cerebral atrophy was noted in only 20.5% of the patients along with skin changes and CT brain calcification noted in 12% of the patients. Our cases showed similar findings supporting the classical neuroimaging finding

Table 2 - Timeline of a 7 year old girl normal birth history and development. she started having symptoms from the age of 5 years. No family history of any neurological illness.

Date	Presentation	Diagnostic Tests	Intervention
15 March 2017	Right focal seizures with secondary generalization 4 attacks in one week	CT brain normal	Sodium valproate started
20 July 2017	Complex partial seizures. Child was seizures free until April 2018	EEG showed spike wave activity over the left centro temporal area.	Sodium valproate dose increased 40mg kg/day
25 March 2018	Complex partial seizures 4-5 attacks daily for 2 weeks.	CT brain, left tempora lobe calcification.	Oxcarbazepine started 20mg/kg/day
18 April 2018	Generalized tonic clonic seizures	The MRI showed hemiatrophy of the left cerebral hemisphere with signal intensity in the left temporal lobe	Dose oxcarbazepine increased to 40mg/kg/day and sodium valproate phased out.
25 April 2018	Hyperpigmentation and hardening of the skin in addition to alopecia over the left side of face	Complete hemogram, liver function test and renal function test revealed normal values. ESR and CRP were normal. C3, C4 normal. ANA, P-ANCA, C-ANCA were negative.	Prednisolone 2 mg/kg/day for 2 weeks then tapered to 1 mg/kg/day for one year and Phased out.Methotrexate 0.5 mg/kg/day started.
18 June 2018	Complex partial seizures		Levetiracetam 20mg/kg/Day started.
17 August 2018	Complex partial seizures	EEG showed mild epileptiform activity over the left centro temporal area.	Dose increase 40 mg/kg/day along with oxcarbazepine.
Until now	Seizure free and no progression of hemi facial atrophy.	Every 3 months follow-up with CBC, LFT, RFT all normal.	Methotrexate 0.5 mg/kg/wk still continuing.

CT - computerized tomography, MRI - magnetic resonance imaging, MRA - magnetic resonance angiography, MRV - magnetic resonance venography, ESR - erythrocyte sedimentation rate, CRP, - C reactive protein, LFT - liver function test, RFT - renal function test, CSF - cerebrospinal fluid, C3, & C4 - complement level 3 & 4, ANA - antinuclear antibodies, P-ANCA - Perinuclear anti-neutrophil cytoplasmic antibodies, C-ANCA - cytoplasmic anti-neutrophil cytoplasmic antibodies, ACE - angiotensin converting enzyme, MELAS - miotochondrial encephalo myopathy, lactic acidosis and stroke, MERFF - myoclonic epilepsy with ragged red fibers, MR - magnetic resonance, EEG - slectroencephalogram, CBC - complete blood count

of Parry-Romberg syndrome. Electroencephalogram is abnormal in 48% of his study and our cases both had EEG changes.[5] Cerebrospinal fluid protein was mildly elevated in our case 1 suggestive of inflammatory process which is unusal according to Vix et al,[5] but in other studies mildly elevated protein is noted.[2]

Guerrerosantos et al,[10] classified Parry-Romberg syndrome into 4 types: type 1 & 2 (mild) involvement of the skin and soft tissue of the face, type 3 & 4(severe) involvement of bone and cartilage.

The common neurological manifestations includes trigeminal neuralgia, migraine, facial paresthesia, and seizures.[2] Occasionally vascular malformations and intracranial aneurysms are observed. Skin biopsies may reveal epithelial and dermal tissue atrophy resembling linear scleroderma.

There is no definitive cure for Parry-Romberg syndrome and multidisciplinary team approach is needed for management. The active stage of the disease may be treated with corticosteroids and immunosuppressant therapies. Milder types (1 & 2) treated with autologous fat graft and severe types(3& 4) needed surgical reconstruction once disease is stabilized.[2]

In conclusion, Parry-Romberg syndrome is a rare acquired neurocutaneous disorder with progressive unilateral facial atrophy of unclear etiology. We report 2 cases of Parry-Romberg syndrome with different neurological manifestations from the Kuwait though cases has been reported with Middle East without neurological symptoms. Skin examination is essential in any patient with unexplained neurological symptoms. Localized scleroderma can be accompanied by neurological symptoms. Active disease can be managed with immunosuppressant.

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