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Case Report

A rare case of hypomelanosis of Ito with enlargement of Virchow-Rabin spaces in a 10-year-old child with symptoms of seizures

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Abstract: Hypomelanosis of Ito (HI) syndrome is a complex neuro-dermatological disorder that affects many organs in the body, including the skin, brain, eyes, and skeleton. This disease has been reported to present with seizures in a few rare cases. Seizures are seen in all age groups but are more common in children and the elderly. Virchow-Robin spaces (VRSs) are spaces around small arteries and the arteries that pierce the surface of the brain and are spread throughout the rest of the brain. As individuals age, the number and size of VRSs increase. A relationship between dilated VRSs and neuropsychiatric disorders has been observed above a 2 mm threshold. The patient is a 10-year-old child who was referred to the neurology ward of Imam Hossein Children's Hospital in Isfahan about 2.5 months ago due to seizures. The last seizure occurred four days before the visit, and the patient was sent for a brain computed tomography (CT) scan, which revealed diffuse bilateral hypopigmented lesions in the brain's white matter. The results of the para-clinical tests were relatively unremarkable. In the early stages of hospitalization, the child received treatment such as fluid therapy and anticonvulsant drugs to stabilize their vital condition. The patient's para-clinical tests, including brain CT, electroencephalogram, complete blood count, liver function test, and magnetic resonance imaging, showed the presence of HI syndrome and bilateral diffuse hypopigmented lesions in the white matter.

Keywords: Hypomelanosis of Ito, seizure, Virchow-Robin space

Introduction

Hypomelanosis of Ito (HI) syndrome is a complex neuro-dermatological disorder that affects many organs in the body, including the skin, brain, eyes, and skeleton. This disease is caused by a skin abnormality that affects areas of the body with low or absent pigmentation in a bilateral, unilateral, or circular manner [1]. The diagnostic criteria for HI include non-hereditary cutaneous hypopigmented linear streaks or patches involving more than two body segments that appear at birth or in the first few months of life, as well as one or more neurological or musculoskeletal manifestations. The diagnosis of HI is made through a computed tomography (CT) or magnetic resonance imaging (MRI) scan of the head [2].

Hypomelanosis of Ito (HI) syndrome is associated with several disorders, most commonly affecting the central nervous system, bones, and eyes. The main clinical presentations of HI include strabismus, hearing problems, hirsutism, scoliosis, seizures, intellectual disability, and mouth or tooth problems [1]. It affects both men and women equally and is typically a recurrent disorder with a low chance of recurrence [3, 4]. The incidence and prevalence of HI per birth and individual have been reported to be 7540.1 and 82000.1, respectively. Rare cases of HI have been reported with seizures [5, 6].

Seizures are the most common treatable neurological disorder in children. The causes of seizures include a wide range of diseases involving

the nervous system. Seizures result from a malfunctioning electrical system in the brain caused by the depletion of cerebral cortical neurons. Symptoms of seizures depend on the location of the disorder in the brain and may include a lack of awareness of the environment, involuntary movements, perceptual changes, behaviors, emotions, and posture of the patient [7, 8].

Seizures are observed in all age groups but are more frequent in children and the elderly. Approximately one in ten children will experience a seizure during the first 16 years of life, and the highest incidence of seizures in children is observed during the first few months of life. The causes of seizures in children vary depending on their age, with birth injuries being the most common cause in young infants, including intracranial injury, bleeding, anoxia, or congenital brain abnormalities [7, 9].

Treatment of HI is based on the severity of clinical manifestations. According to the available evidence, cutaneous manifestations of HI do not necessitate treatment and may be covered with makeup if desired by the patient [2, 5]. Neurological manifestations, such as seizures, can be managed with valproic acid [2]. The prognosis is influenced by the patient's symptoms and disease-related complications.

Virchow-Robin spaces (VRSs) are spaces around small arteries and the arteries that penetrate the surface of the brain and extend throughout the brainstem, initially described in the works of Rudolf Virchow and Charles Philipp Robin, a German pathologist and anatomist [10].

In the deeper regions of the brain, VRSs are surrounded by the basal ganglia, with the blood vessels' outer surface in the center. The soft tissues of the VRSs form a closed space filled with fluid that separates the cerebrospinal fluid from the spinal cord. They are also observed in the normal population. Small VRSs (less than 2 mm) are observed in all age groups, and their number and size (above 2 mm) increase with age. Some studies have identified an association between dilated VRSs and neuropsychiatric disorders. Therefore, based on the current literature, we present a case report of a 10-year-old child who was referred to the hospital with seizures.

Case report

This report is on a 10-year-old child from Iranian Kurdistan who was referred to the neurology ward of Imam Hossein Children's Hospital in Isfahan due to four seizure episodes. The patient did not have a history of movement disorders. We obtained written informed consent from the parents.

The presence of bilateral diffuse hypopigmented lesions in the white matter of the brain observed in the CT scan may suggest a neurological disorder, which may explain the patient's seizures and developmental delay following birth. The fact that the seizures occurred during sleep may indicate a potential link between the seizures and the patient's sleep patterns. It is important to conduct further tests to determine the underlying cause of the hypopigmented lesions and seizures, as well as to develop an appropriate treatment plan.

The clinical examination was normal except for the presence of hypopigmented lesions in the limbs and trunk. The electroencephalogram (EEG) was reported as abnormal due to paroxysmal recharges. The patient was started on fluid therapy and anticonvulsant drugs followed by the preclinical measures, including brain CT, EEG, complete blood count (CBC) and liver function test (LFT).

The patient received normal saline for fliud therapy based on the following instruction:

- For the first 10 kg body weight: 100 ml/kg/day.
- For the second 10 kg body weight: 50 ml/kg/day.
- For each additional kg body weight: 20 ml/kg/day.

As the patient weighted 38 kg, she received 1860 ml/day fluids.

For anticonvulsant, the patient received valproic acid 10 mg/kg/day, given in divided doses.

Table 1. Para-clinical test results of the case

Parameter (unit)	Result	Normal range
Sodium (mEq/L)	135-145	140
Potassium (mEq/L)	3.5-5.5	4.3
Aspartate transaminase (units/L)	<37	38
Alanine transaminase (units/L)	<41	29
Amylase	<100	39
Lipase	<60	34
Blood urea nitrogen (mg/dL)	4-20	9.4
Creatinine (mg/dL)	0.5-1.5	0.6
Blood sugar (mg/dL)	70-140	100

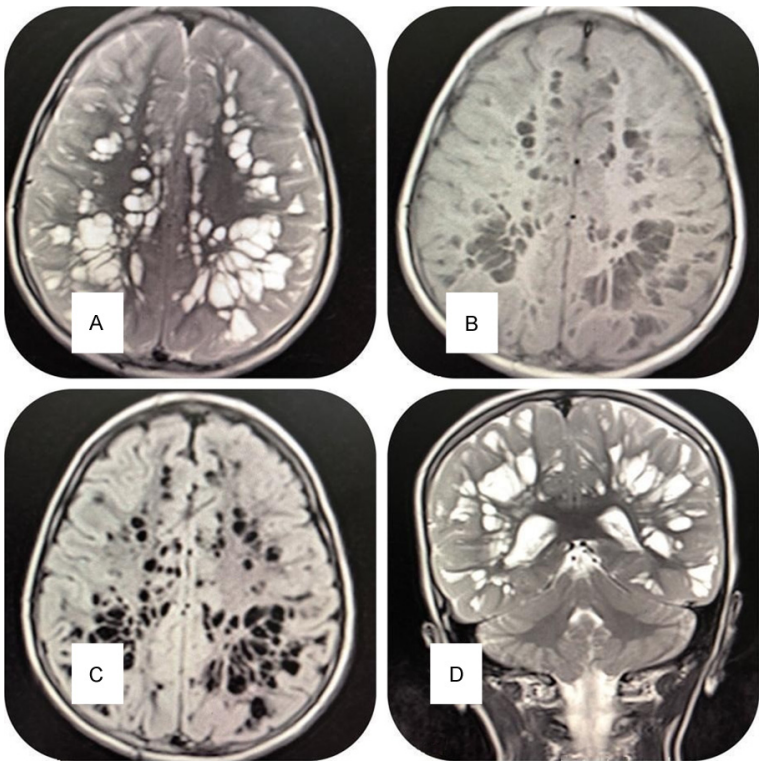

Figure 1. Magnetic resonance imaging (MRI) images. (A) Axial T2-weighted, (B) axial T1-weighted, (C) axial Fluid attenuated inversion recovery (FLAIR), (D) coronal T2-weighted images show numerous variable cystic like intraparenchymal lesions with cerebrospinal fluid signal in all supratentoria lobes in line with dilated Virchow-Rabin Spaces.

The para-clinical information displayed in **Table 1** which is almost normal results.

Imaging findings

Non-contrast MRI of the brain was performed on the second day of admission. Multiple dilated Virchow-Rabin spaces were seen (**Figure 1**). Enlarged perivascular spaces have been reported in various settings, like mucopolysaccharidoses disease (Hurler and Hunter disease), muscular dystrophies, and hypertensive encephalopathy. However, the diagnosis of HI was proposed based on the patient's age, clinical history, and hypopigmented lesions on his body.

The diagnosis of this case was mainly based on the association of clinical presentations and imaging studies. This case had multiple Virchow-Rabin spaces on the MRI and a history of seizures. The differential diagnosis for this condition includes HI syndrome and Mucopolysaccharidosis [5]. Therefore, this case was diagnosed with HI syndrome. We should note that no further investigations and diagnostic measures were used for this case because of a low family socio-economic condition.

Follow-up of the case 3 months after admission showed improved clinical conditions and controlled seizures with anti-convulsant pharmacotherapies.

Follow-up care for patients with Hypomelanosis of Ito typically involves regular monitoring to assess the progression of the disorder and the effectiveness of treatment.

Some of the indexes and examinations that can be used to judge the recovery of patients with Hypomelanosis of Ito during follow-up include [3, 4]:

- Skin examination: Hypomelanosis of Ito causes distinctive patterns of skin discoloration that can be used to track the progression of the disorder over time. Regular skin examinations can help to identify new areas of hypo- or hyperpigmentation and evaluate the effectiveness of treatments such as topical corticosteroids or laser therapy.

- Neurological evaluation: Many patients with Hypomelanosis of Ito have neurological symp-

toms such as developmental delay, seizures, and intellectual disability. Regular neurological evaluations can help to track the progression of these symptoms and assess the effectiveness of treatments such as anticonvulsant medications or physical therapy.

● Imaging studies: Imaging studies such as MRI or CT scans can be used to evaluate changes in the brain or spinal cord that may be associated with Hypomelanosis of Ito. These studies can be used to assess the effectiveness of treatments such as surgery or radiation therapy.

Further imaging follow-ups are also planned for the patient.

Discussion

HI represents a heterogeneous group of primary diffuse cutaneous neurological disorders resulting from chromosomal mosaics. Nervous system manifestations may include cognitive impairment, seizures, spasms, cerebellar ataxia, and microcephaly. Additionally, the abnormalities observed in MRI of people with HI usually include white matter lesions, multiple cerebral infarctions corpus callosum hypoplasia, and enlargement of the Virchow-Robin spaces. HI is still a challenging disorder to diagnose by pediatric neurologists and a controversial topic in the medical literature [5]. The current study aimed to present a case of HI in a 10-year-old child with symptoms of seizures and enlargement of the VRSs of the brain who was referred to Imam Hossein Children's Hospital. The patient's para-clinical results, including brain CT, EEG, CBC, and LFT, as well as MRI, showed the presence of this disease.

The diagnosis of HI is mainly based on clinical presentations, head CT scans or MRIs, X-rays of patients with skeletal problems, and genetic testing [1, 2]. Genetic testing is the final option in suspicious cases and confirms the diagnosis. As mentioned earlier, the diagnosis of this case was based on clinical presentations and imaging studies, and genetic testing was not conducted due to the socio-economic problems of the family. The distribution of HI syndrome and diffuse hypodense lesions has been bilateral in the brain's white matter. Although the initial report on HI in 1952 described it as a pure skin disease, subsequent cases and studies have shown a 33 to 94% association with multiple and sometimes severe skin manifestations, mainly affecting the central nervous system and musculoskeletal systems. HI can affect many organs, and several presentations, such as seizures and intellectual disability, have been reported.

Uçar et al. reported a case of HI in a seven-month-old infant who presented to the hospital with symptoms of seizures, which is consistent with the current study's findings. In a similar study, Çiğdem İlter Uçar and colleagues reviewed a case report of a 16-year-old girl with a one-year history of headache and unilateral HI lesions in the abdomen and lower extremities, along with unilateral brain lesions [11].

Steiner and colleagues investigated abnormal MRI brain findings in 12 patients with HI over the past 14 years. Based on the MRI results of this study, abnormalities such as dilatation of the Virchow-Robin spaces or brain atrophy were reported in 5 patients with HI. This study highlighted the existence of HI-related abnormalities in patients [11].

In another study, Souza and colleagues reported on a case of HI in a 52-year-old woman with a 10-year history of memory loss and dysfunction. Examination of the patient revealed pigmented rings and linear streaks following Blaschko's lines in various parts of the body, typically associated with HI. MRI findings of the patient's brain showed large, prominent Virchow-Robin spaces. In this study, Souza and colleagues demonstrated that HI may be linked to adult dementia and enlarged Virchow-Robin spaces [12].

Generally, the VRS space is bilateral, but it can also be one-sided in some cases. However, bilateral involvement is primarily associated with HI. Steiner and colleagues demonstrated in a case-series study that skin lesions in two children were related to bilateral brain involvement. One of the cases showed cerebellum with corpus callosum hypoplasia, while the other case only had VRS.

In another study, Albuja and colleagues reported that cutaneous manifestations are present in 100% of individuals with HI, and seizures are the second most important neurological manifestation. According to Albuja et al., seizures have been reported in 11% to 50% of HI patients. In this study, more than 50% of patients with HI had specific abnormalities within the white matter that could be detected by MRI [13].

The MRI findings in Albuja et al.'s study revealed small, clear, multifocal, and symmetrical signal abnormalities in the white matter surrounding the ventricles and subcortical walls of both hemispheres. These lesions, present in the first months of life, were not related to the patients' age and remained constant over time. Additionally, a similar finding in individuals with isolated HI has been reported to be pathologically associated with open spaces of VRS. The authors of this study reported a child with normal intelligence and non-neurological manifestations with extensive white matter changes. Other prominent abnormalities detected by CT and MRI in patients with isolated HI include local or general brain, brainstem, or cerebellum atrophy, dilation of the cerebral ventricles, and hemispheric asymmetry. Cerebellar hypoplasia, corpus callosum hypoplasia, and gray matter heterotopic Lissencephaly have been associated with intraventricular cystic lesions and arterial abnormalities [13].

Conclusion

Overall, this case report showed the presence of HI syndrome and bilateral diffuse hypodensities in the brain's white matter. Also, the VRS space can be isolated findings associated with skin lesions.

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Disclosure of conflict of interest

None.

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