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Case Report

Neuroimaging findings in Griscelli syndrome type 2 with primary neurological presentation

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Abstract. We report the radiologic findings in two children with Griscelli syndrome who presented mainly with neurologic findings. Both children were born to consanguineous parents, had normal birth and developmental histories; both had silvery gray hair from the time of birth. The first child presented with symptoms of increased intracranial pressure and cerebellar ataxia; the second child with cerebellar ataxia alone. Microscopic examination of the hair in both the children demonstrated the characteristic melanin clumps suggestive of Griscelli syndrome. Magnetic resonance imaging of the brain in the first child demonstrated multifocal white matter hyperintensities in the cerebrum and diffuse white matter hyperintensities in the cerebellum, with intense contrast enhancement. In the second child, signal changes were confined to the cerebellum and spinal cord. The first child succumbed to rapidly progressive increased intra-cranial pressure; partial autopsy revealed necrotizing lesions involving the cerebellar hemispheres bilaterally which corresponded to the neuroimaging abnormalities. Histology revealed diffuse histiocytic infiltration of the parenchyma. Griscelli syndrome type 2 should be a diagnostic consideration in a child with silvery hair, neurological deterioration and enhancing multifocal white matter signal intensity changes

Keywords: Griscelli syndrome, silvery hair, cerebellar leukoencephalopathy, melanin clumps

1. Introduction

Griscelli syndrome (GS) is a rare autosomal recessive immunodeficiency syndrome associated with deficient pigmentation of the skin and hair, large clumps of pigment in the hair shafts and accumulation of melanosomes in melanocytes [1]. It is classified into three different subtypes, all of which show similar pigment dilution. The second type, GS type 2 (GS2) [MIM 607624], is caused by a mutation in the RAB27A gene [2]. Most patients with GS2 develop an uncontrolled T-lymphocyte and macrophage activation syndrome known as the hemophagocytic syndrome or hemophagocytic lymphohistiocytosis, leading to death in the absence of chemotherapy and bone marrow transplantation [2]. This accelerated phase is characterized by lymphocytic infiltration of the visceral tissues including the central nervous system (CNS) [3]. Rarely, neurological features can be the sole manifestation at

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presentation; this may pose a diagnostic challenge [3–5]. In the present report, we describe the magnetic resonance imaging (MRI) findings in two patients with GS2 who presented with only neurological manifestations; i.e without immunological abnormalities or organomegaly.

2. Patients and methods

2.1. Patient 1

This 4-year-old boy was the third child of consanguineous parents and had a normal birth and developmental history prior to presentation. He was noted to have fine gray hair at birth. He presented with a history of recurrent headache, vomiting, drowsiness and unsteady gait that lasted for one month. There was no associated fever or seizures. Family history was negative for similar illness. There was no history of any recurrent infections or hospitalizations.

Examination showed a dull and irritable child with silvery gray hair. He had normal growth parameters. On neurological examination, he had normal cranial nerves, brisk muscle stretch reflexes and bilateral extensor plantar responses. He had cerebellar signs in the form of finger to-nose incoordination, stance and gait ataxia. Opthalmological examination revealed normal optic disc and retina. Systemic examination did not reveal any lymphadenopathy or hepatosplenomegaly. Evaluation showed microcytic hypochromic anemia and normal biochemical parameters. High performance liquid chromatography of the blood sample revealed a nonspecific increase in taurine.

MRI was done in a Siemens-Magnetom Vision 1.5 Tesla MRI scanner (Erlangen Germany). Spin echo T1-weighted images in axial and sagittal planes were taken with the following parameters: repetition time [TR] = 650 ms, echo time [TE] = 14 ms, with an acquisition (ACQ) time of 2.5 mt, matrix of 256 × 256, and a 230 mm field of view (FOV). T2-weighted images (TR = 4000 ms, TE = 120 ms) were acquired in axial and coronal planes. Fluid attenuated and inversion recovery (FLAIR) sequences were obtained in axial plane: (TR = 9000 ms, TE = 119 ms, inversion time = 2457 ms, slice thickness, 5 mm.).

T2-weighted and FLAIR images showed mutiple hyperintense lesions of the cerebral and cerebellar white matter (Fig. 1A–F). In the supratentorial compartment, scattered discrete white matter signal changes were

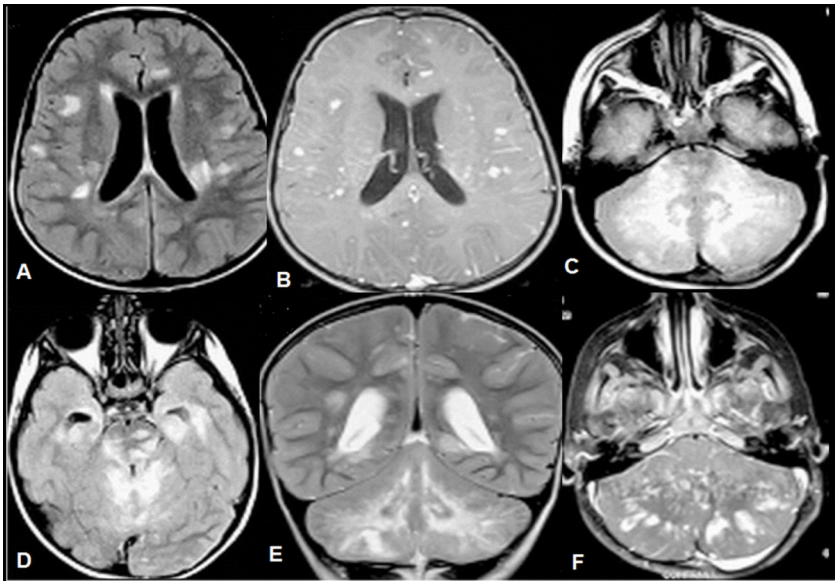

Fig.1. Magnetic resonance imaging of the brain in patient 1. (A) Fluid-attenuated inversion recovery axial view demonstrating mutifocal white matter hyperintensities involving periventricular, deep- and sub-cortical white matter. (5 mm thick, repetition time = 9000 ms, echo time = 119 ms, inversion time = 2457 ms, matrix of 256 × 256, field of view = 230 mm). (B) On contrast-enhanced T1-weighted images the lesions show intense contrast enhancement. (Repetition time = 650 ms, echo time = 14 ms, acquisition time of 2.5 mt, matrix of 256 × 256 and a 230 mm field of view). (C) T2 -weighted (Repetition time = 4000 ms, echo time = 120 ms) axial and coronal images (C and E) and fluid-attenuated inversion recovery (Repetition time = 9000 ms, echo time = 119 ms) axial image. (D) Signal changes in the brainstem, middle cerebellar peduncle, cerebellar white matter and dentate nuclei. On contrast, enhanced T1-weighted axial images the lesions show intense contrast enhancement (F).

present in the subcortical, lobar and periventricular white matter. These lesions demonstrated dense and discoid contrast enhancement (Fig. 1B). The posterior fossa showed lesions involving the middle cerebellar peduncle, cerebellar white matter and hilus of the dentate nuclei bilaterally and symmetrically and scattered lesions in the brainstem. (Fig. 1C–E) These lesions demonstrated similar contrast enhancement (Fig. 1F).

In view of the history of subacute onset of neurological symptoms and signs along with multifocal discrete white matter signal changes, a diagnosis of demyelinating disease was considered and the child was treated with intravenous methyl prednisolone (30 mg/kg/d) and other supportive measures. His sensorium progressively deteriorated after admission. A repeat computerised tomographic (CT) scan showed hydrocephalus which necessitated a ventricular tap and external ventricular drain. Ventricular cerebrospinal fluid (CSF) showed three lymphocytes and normal glucose and protein. He expired on the tenth day of hospitalization.

A partial autopsy, confined to examination of the brain alone, was performed following written informed consent of close relatives. Gross examination of the brain revealed necrotizing lesions in cerebral and cerebellar white matter that corresponded to the lesions on MRI. These lesions were seen as multiple small granular pale necrotic zones involving bilateral internal capsule in asymmetric fashion, extending into the adjacent medial temporal whiter matter and amygdala (Fig. 2A and B). In the posterior fossa, bilateral cerebellar hemispheres revealed granular breakdown (Fig. 2C and D) in addition to discolored foci of necrosis involving the pontine tegmentum and cerebellar dentate nucleus. Histology of these lesions revealed lymphohistiocytic infiltration with breakdown of the parenchyma. Microscopic examination of the hair revealed large clumps of melanin along the shaft of the hair confirming the diagnosis of GS.

2.2. Patient 2

This six-year-old boy, born to consanguineous parents with normal birth and developmental history, presented with acute onset of gait difficulty and slurring of speech following a diarrheal illness. He was evaluated in a peripheral hospital with a diagnosis of postinfectious demyelination. He received a course of parenteral methylprednisolone (30 mg/kg/d) followed by oral steroids (1 mg/kg/d) with substantial improvement. One month later while on tapering dose of steroids, the

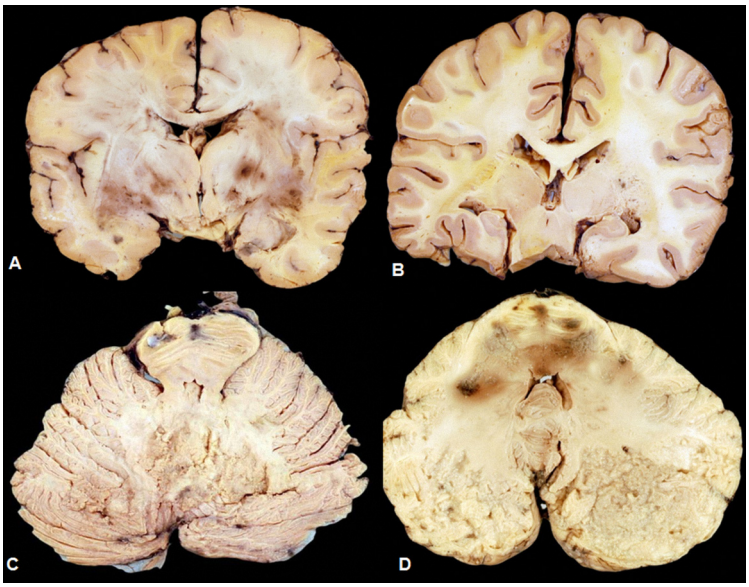

Fig. 2. Gross brain examination: Coronal slices of brain at the level of the infundibulum (A) reveal patchy hemorrhagic lesions involving bilateral internal capsule, extending to the putamen and amygdala on the right side. More posteriorly, at the level of the crus cerebri (B) there is softening and breakdown of the posterior limb of the internal capsule on left side and adjacent thalamic nuclei. Horizontal sections of the brain stem (C and D) reveal breakdown and necrosis of cerebellar vermis and the cerebellar hemispheres posteriorly, in addition to patchy hemorrhages along the pontine tegmentum, extending into the transverse pontine fibres and the middle cerebellar peduncle.

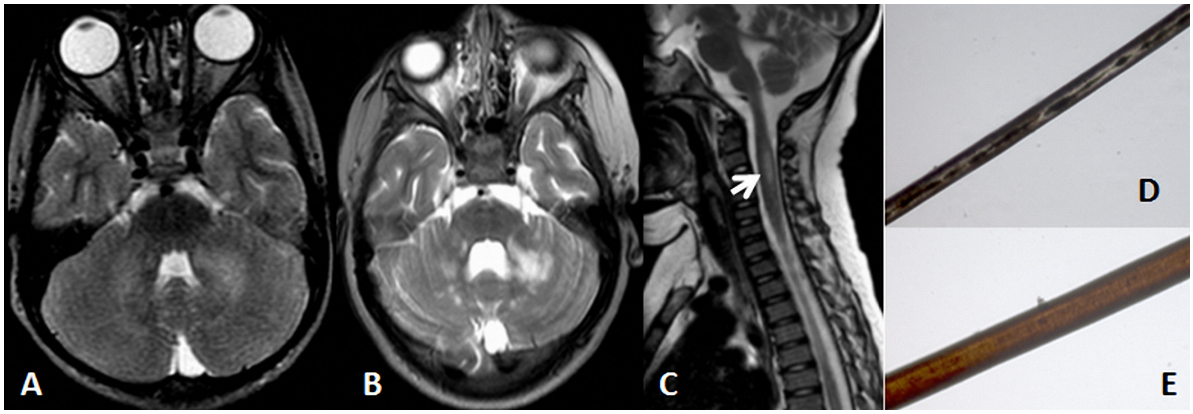

Fig. 3. Magnetic resonance imaging brain in patient 2. (A) Axial T2 weighted images demonstrate bilateral symmetrical signal changes in cerebellar white matter at initial presentation (Repetition time = 4000 ms, echo time = 120 ms acquisition time of 2.5 mt, matrix of 256 × 256, field of view = 230 mm). (B) Axial T2 weighted images demonstrate asymmetric signal changes in the cerebellar white matter, one month after the initial presentation. (5 mm thick, 0.5 mm gap, flip angle = 90 degrees, repetition time = 3000 ms, echo time = 80 ms, voxel size = 0.71 mm × 0.88 mm × 5.38 mm, field of view = 240 mm). (C) Magnetic resonance imaging of the spinal cord. T2 weighted sagittal view of spinal cord shows a hyperintense lesion in the cervical region. (3-milimeter thick, 0.3 mm gap, flip angle = 90 degrees, repetition time = 3000 ms, echo time = 120 ms, voxel size = 0.75 mm × 1.04 mm × 3 mm, field of view = 290 mm). (D) Light microscopic examination of the hair shafts showing variably sized aggregates and clumps of melanin pigment. (E) Normal hair shaft for comparison.

symptoms reappeared and he was referred to our hospital.

On examination, the patient had Cushingoid features, silvery grey hair, eye brows, and eye lashes. His growth parameters were within normal limits. On neurological examination, he was shown to have normal cranial nerves, muscle tone, and power, but he had exaggerated stretch reflexes and bilateral extensor plantar response. He demonstated a lack of coordination, with the finger-to-nose task bilaterally and gait ataxia. His sensory sytem examination was normal. There was no lymphadenopathy or hepatosplenomegaly.

Blood tests showed normal haemogram, biochemical parameters and immunoglobulin levels. Bone marrow examination did not show hemophagocytosis. Ultrasonogram of the abdomen was normal. CSF examination showed 19 cells/mm^3 with protein of less than 10 mg% and glucose of 72 mg%. CSF cytospin revealed numerous degenerated cells and few lymphocytes.

Review of the original MRI performed, in the peripheral center, showed bilateral symmetrical hyperintensities of the cerebellar white matter (Fig. 3A) and focal hyperintensities in the spinal cord on T2- weighted images. Contrast study was not obtained at this time. On follow-up MRI at this institution there were hyperintensities noted in the bilateral cerebellar white matter on T2-weighted and FLAIR images. (Fig. 3B) Faint peripheral enhancement was seen on the left side. Spinal cord showed short segment T2 hyperintensities involving the central cervical cord at C2, C3 levels (Fig. 3C) Microscopic examination of the hair showed clumps of melanin along the shaft of the hair suggestive of GS. (Fig. 3D and E).

3. Discussion

The two patients described in the current report presented with acute to subacute onset of neurological symptoms mainly characterized by ataxia. At the time of presentation both of them did not have evidence of systemic symptoms. A wide range of possible disorders should be considered in a child presenting with neurologic symptoms and white matter lesions on brain MRI [6]. The first diagnostic consideration in a child who presents with focal neurological deficits and multifocal white matter lesions on MRI would be that of a primary demyelinating disease such as acute disseminated encephalomyelitis or pediatric multiple sclerosis. Contrast enhancement of the lesions may suggest the possibility of infectious or non-infectious inflammatory diseases in addition. However, the uniform intense contrast enhancement of all the lesions as noted in the first child is rare in primary demyelinating diseases where a partial or complete rim enhancement is more common [7]. Moreover, topographical distribution of the lesions such as bilateral symmetrical involvement of the cerebellar white matter and absence of corpus

callosal involvement were odd for acute disseminated encephalomyelitis and pediatric multiple sclerosis.

Granulomatous disorders of infectious etiology are important causes of multiple ring-enhancing or disc-enhancing lesions in tropical countries and include tuberculomas, fungal infections, neuro-brucellosis, neuro-borreliosis and toxoplasmosis [6,7]. Additionally, leptomeningeal disease and cerebrospinal fluid pleocytosis may point to an infectious etiology.

The multifocal discrete white matter signal changes also raised the suspicion of other acquired white matter diseases in children such as a primary CNS vasculitis, secondary CNS vasculitis like CNS lupus and Behcet's disease, and granulomatous diseases like neurosarcoidosis [8]. The intense contrast enhancement of the lesions also suggested a diagnosis of primary or secondary CNS lymphoma [6,7]. Other differential diagnoses to be included are mitochondrial disorders including polymerase gamma-related disorders, mitochondrial encephalopathy with lactic acidosis, stroke-like episodes and Leber's hereditary optic neuropathy [8]. A patchy contrast enhancement sometimes can be observed in these patients, but the type of intense contrast enhancement of all the lesions as seen in the first patient are never observed in mitochondrial disorders.

The bilateral symmetrical involvement of the cerebellar white matter in the first patient fulfilled the MRI criteria for a cerebellar leukoencephalopathy, namely diffuse cerebellar white matter signal changes involving both the corpus medullare and the hilus of the dentate nucleus leaving the apparently unaffected dentate nucleus prominently visible in between and predominance of cerebellar white matter abnormalities over cerebral white matter abnormalities [9]. Such a finding has been correlated with a diagnosis of histiocytosis. Although the cerebellar white matter signal changes were not as prominent as in the first patient, the second child also had dominant cerebellar white matter signal changes along with spinal cord involvement. Other diseases with predominant cerebellar leukoencephalopathy include giant axonal neuropathy and cerebrotendinous xanthomatosis which were unlikely in view of the absence of suggestive morphological features.

Both of our patients had silvery gray hair and the characteristic melanin clumps in the hair shafts on microscopy, suggesting the diagnosis of GS. The other disorder with silvery hair is GS type 1(GS1), previously known as Elejalde syndrome. GS1 patients presents with primary and severe neurologic impairment. Immunodeficiency and the accelerated phase is not part of the clinical picture in GS1 patients. Our patients did not have developmental delay or mental retardation prior to the onset of regression, thus ruling out GS1. The morphology of melanin clumps ruled out Chediak-Higashi syndrome, another disorder with hypo- pigmentation and immunodeficiency, where the fine melanin clumps are noted instead of large clumps. In addition, a peripheral smear did not show any evidence of leukocyte granulation.

The pathological examination of the brain in the first patient showed necrotizing lesions corresponding to the lesions on MRI and histiocytic infiltration of the parenchyma thus further supporting the diagnosis. Even though genetic testing was not done, morphological and pathological findings constituted sufficient evidence for the diagnosis.

The spectrum of neurological involvement in GS is varied. In GS2, the lymphohystiocytic infiltration of the brain occurs in the accelerated phase resulting in seizures, hypertonia, hyperreflexia, cerebellar signs, hemiparesis, increased intra cranial tension and loss of acquired milestones [10,11]. There are limited reports of GS2 presenting with primary neurological manifestations [3–5]. The clinical presentations in these reports included deterioration in sensorium, seizures, encephalitis- like illness and ataxia without other signs of accelerated phase. MRI demonstrated multiple contrast enhancing lesions of the white matter involving both the cerebellar hemisphere and the supratentorial compartment, which is similar to the present report.

The first patient in the current study had obstructive hydrocephalus during the course of his illness which required ventriculostomy. This complication has been reported as the initial presentation in GS2 [3]. Two of the six patients reported by Klein et al. [10] also had ventriculo-peritoneal shunts inserted. All the six patients had other features of accelerated phase and neurological manifestations including seizures, signs of intracranial hypertension and cerebellar signs. These reports, and the current report, reinforce the occurrence of obstructive hydrocephalus as a life threatening complication of either the accelerated phase or as an initial manifestation in GS2.

The dominant involvement of the cerebellar white matter with contrast enhancement in GS has been noted in earlier reports. Brismar and Harfi [12] described this syndrome as a rare entity with prominent posterior fossa white matter changes in a cohort of five patients. The lesions involved the posterior fossa white matter predominantly, but also had periventricular and diffuse white matter involvement in some in addition

to atrophy. The authors suggested that this syndrome should be considered in young children with rapidly progressive white matter changes especially involving the cerebellum. Other radiologic imaging findings include bilateral basal ganglia signal changes, ventricular dilatation, and calcification involving basal ganglia [10,11,13]. Another noteworthy observation was the spinal cord signal changes in the second patient. Spinal cord signal changes have been rarely reported in this syndrome [3]. Multifocal white matter involvement in brain and spinal cord in the absence of systemic signs may lead to a diagnosis of demyelination as in our patients.

The clinical course of GS2 patients is complicated by recurrent accelerated phases and the prognosis is poor. Remission may be achieved with chemotherapy or immunosuppressive therapy, but early relapses are common. Allogenic haematopoietic stem cell transplantation remains the only curative treatment in this disease [5,10].

In conclusion, this report reinforces the idea that CNS manifestations can be the first presentation in patients with GS2. GS should be included in the differential diagnosis for children presenting with cerebral and cerebellar white matter demyelination with contrast enhancement. Presence of silvery hair is a diagnostic clue and may facilitate early referral for intervention.

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