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CASE REPORT

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Neuroimaging abnormalities in Griscelli's disease

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Abstract Griscelli's disease is a rare autosomal recessive immunodeficiency syndrome. We report a 7-1/2-month-old white girl who presented with this syndrome, but initially without neurological abnormalities. Initial CT of the brain was normal. Despite haematological remission with chemotherapy, she developed neurological symptoms, progressing to coma. At this time, CT showed areas of coarse calcification in the globi pallidi, left parietal white matter and left brachium pontis. Hypodense areas were present in the genu and posterior limb of the internal capsule on the right side, as well as posterior aspects of both thalami, together with minimal generalised atrophy. MRI revealed areas of increased T2 signal and a focal area of abnormal enhancement in the subcortical white matter. Griscelli's disease should be added to the list of acquired neuroimaging abnormalities in infants.

Keywords Griscelli's disease · Neuroimaging · Brain calcification · Haemophagocytosis

Introduction

Griscelli's disease (GD) is a rare autosomal recessive immunodeficiency syndrome associated with deficient pigmentation of skin and hair, large clumps of pigment in hair shafts and accumulation of melanasomes in melanocytes [1]. Most patients develop an uncontrolled T-lymphocyte and macrophage activation syndrome (known as haemophagocytic syndrome, HS) in the first year of life, leading to death in the absence of chemotherapy and bone marrow transplantation [2]. Severe neurological disorders, varying from mild cognitive impairment to fatal degeneration due to cellular infiltration of the brain, are a feature of the disease. In 1997, the GD locus was mapped on chromosome 15q21 (*MYO5A*), and recently mutations in a second gene (*RAB27A*) in the same chromosomal region were also identified [3].

In familial haemophagocytic syndromes, brain involvement on MR images is progressive and consists of parenchymal atrophy, diffuse abnormal signal intensity in the white matter on T2-weighted (T2-W) images, focal hyperintense lesions in both white and grey matter, delayed myelination and parenchymal calcifications [4].

Case report

A 7-1/2-month-old white girl presented with a 2-day history of fever and generalised convulsions. She was pale, had silvery-grey hair and hepatosplenomegaly. A complete blood count showed anaemia (Hb 6.9 g/dl) and thrombocytopaenia (28,000/mm^3). Haematology consultation, examination of the bone marrow, pigment clumps on microscopic examination of the hair, together with parental consanguinity led to the diagnosis of GD in the accelerated phase. An unmodified HLH-94 chemotherapy protocol (daily systemic dexamethasone, etoposide and four doses of intrathecal methotrexate) was administered and rapid complete

clinical and haematological remission was achieved in the third week. Genetic study revealed a missense mutation (A148 C) and 1-bp deletion (del G) in *RAB27* gene, which confirmed the diagnosis.

Febrile convulsions on the first day were controlled and no other neurological manifestation was observed. The cerebrospinal fluid (CSF) showed no pleocytosis and cranial CT showed no abnormality. Intrathecal methotrexate was discontinued due to lack of progressive neurological symptoms and normal CSF examination results. Bone marrow transplantation could not be undertaken. On the third month of follow-up as an outpatient and still on therapy (twice weekly IV pulsed dexamethasone and etoposide, daily cyclosporine), the patient presented with myoclonic jerks and irritability. The CSF showed pleocytosis (15 mononuclear cells/mm^3), slightly increased protein level (60 mg/dl), but culture remained sterile and viral serology test results for EBV-VCA, CMV and herpes viruses were negative. EEG revealed disorganisation with high-amplitude sharp and slow waves. Daily systemic dexamethasone and weekly intrathecal methotrexate were recommenced. Although the myoclonic jerks were controlled with carbamazepine on the ninth day, the patient had rapid neurological deterioration beginning with loss of eye contact and leading to deep coma in 4 weeks.

CT showed areas of calcification in the globi pallidi, left parietal white matter and left brachium pontis (Fig. 1a). Ill-defined hypodense areas were present in the genu and posterior limb of the right internal capsule, as well as posterior aspects of both thalami (Fig. 1b). Minimal generalised atrophy was present. MRI (Fig. 1c) revealed areas of increased T2 signal corresponding to the areas of decreased density on the CT. There were scattered areas of increased T2 signal involving the pars compacta of the substantia nigra bilaterally, patchy areas in both parietal lobes, periaqueductal white matter, external and extreme capsules and frontal subcortical white matter on the right side. Myelination was not delayed. Following IV Gd-DTPA, lesions in the superior aspect of the left cerebellar hemisphere, both basal ganglia and left frontal subcortical white matter showed abnormal enhancement (Fig. 1d). Follow-up CT 1 month later showed increased density of the calcified areas as well as enlargement of the hypodense areas to involve both basal ganglia and greater portions of the thalami.

The patient was lost to follow-up 5 months after diagnosis.

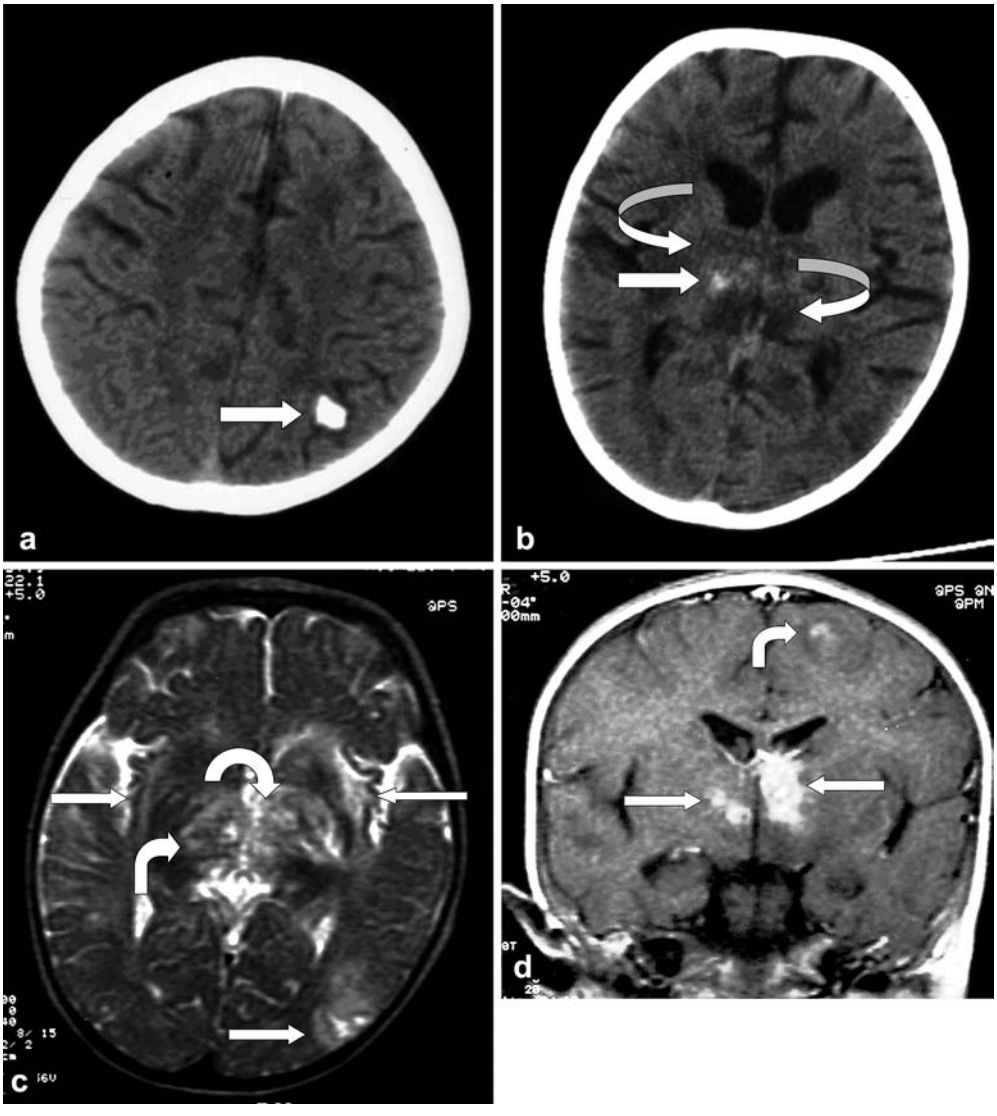

Fig. 1a–d **a** Axial CT shows calcifications in the left parietal subcortical white matter (*arrow*). **b** Axial CT scan at the level of the basal ganglia shows a focus of calcification in the right globus pallidus (*straight arrow*) as well as bilateral hypodense areas (*curved arrows*). **c** Axial T2-W FSE MRI (TR/TE, 4,200/98) shows bright lesions in the subcortical–periventricular white matter (*straight arrows*) as well as deep grey-matter nuclei (*curved arrows*). **d** Coronal T1-W SE image (TR/TE, 400/12) after IV gadolinium shows abnormal enhancement in the basal ganglia and a subcortical lesion (*curved arrow*)

Discussion

Both *MYO5A* and *RAB27A* genes participate in melanosome transport and cause similar clustering of melanin in hair shafts and skin in GD. In patients with the *RAB27A* mutation, HS is characterised by acute onset of uncontrolled lymphocyte and macrophage activation, resulting in haemophagocytosis and infiltration of multiple organs [4]. In a number of patients with familial haemophagocytic lymphohistiocytosis (FHL), mutations in a lytic granule constituent, perforin, were recently identified [5]. Perforin is secreted from cytotoxic T lymphocytes and natural killer cells upon conjugation between effector and target cells and in the presence of calcium. It penetrates the membrane of the target cell where it polymerises to form a cell death-inducing pore. Pore formation leads to destruction of target cells by osmotic lysis and by allowing entrance of the granzymes which trigger apoptosis. Perforin mutations were detected with a somewhat higher prevalence in children whose parents originated from Turkey, and it was suggested that this was due to the higher prevalence of consanguineous marriages in this group. Immune cells obtained from FHL patients remained susceptible to apoptosis induced in vitro by Fas ligation and etoposide [5].

In our patient, the first clinical event involved the bone marrow, liver and spleen; 3 months later, radiological abnormalities and symptoms evinced brain involvement. In GD, *MYO5A* expression and function in the brain tissue has been well documented, but expression of *RAB27A* has not been detected in the brain tissue. Pathogenesis of secondary brain involvement in patients with *RAB27A* mutations still requires explanation and analysis of lysosomal protein expression defect and secretory pathways. Patients with a *MYO5A* mutation, but without HS, may present with early neurological manifestations, such as marked motor development delay and mental retardation – the pure neurological form of GD [3]. Opportunistic infections of low virulence were also suggested as the cause of brain lesions [6], but we could not find serological evidence of a triggering virus.

There was no neurological manifestation at the onset apart from generalised febrile convulsions, which were easily controlled. Cerebral CT and CSF findings were also normal. Although we administered intrathecal methotrexate in addition to systemic chemotherapy, our patient developed neurological manifestations, CSF pleocytosis, basal ganglion calcifications and cerebral atrophy suggesting diffuse lymphocyte, histiocyte and macrophage infiltration. Haddad et al. [7] reported neurological manifestations in 34 patients with HS. In this study, 73% of the patients initially presented with CNS involvement. Four of the nine patients without initial CNS involvement later developed CNS disease. The outcome of the patients treated with systemic and intrathecal chemotherapy and/or immunosuppression was extremely poor; all died following multiple relapses or CNS disease progression. In this study, 100% of evaluable patients developed CNS lesions in the absence of bone marrow transplantation. Despite chemotherapy-induced normalisation of the CSF after initial meningitis, neurological symptoms developed within months, regardless of the chemotherapy regimen and frequency and number of intrathecal methotrexate injections. The authors suggested cytokines and other neurotoxic factors, such as tumour necrosis factor alpha secreted from monocytes and activated leucocytes infiltrating CNS, as causes for alteration of myelination. Infiltrating leucocytes could also activate brain microglial cells and astrocytes, which can also secrete neurotoxic glutamate and free radicals.

Neuroimaging findings of GS and other FHL disorders have been reported in the literature [4, 6] and consist mainly of the following:

- Delay in myelination, which is one of the early findings.
- Basal ganglia lesions are identified as areas of prolonged T1 and T2 signal on MRI.
- Focal white matter changes are seen as areas of low attenuation on CT and prolonged T1 and T2 on MRI, spreading from the peritrigonal regions to the fronto-occipital white matter and centrum semiovale throughout the course of the disease. Cerebellar white matter may also be involved. Focal white- and grey-matter lesions are usually a feature of later stages and they may enhance with contrast medium.
- Atrophy, which is a constant feature of late stages, is diffuse symmetrical and non-specific.
- Calcifications are also a late finding and are more pronounced subcortically and adjacent to areas of white matter involvement. They may assume a gyriform appearance and the cerebellum and deep white matter may also be involved.

In 1992, Brismar et al. [6] described the neuroradiological findings in 11 cases with partial albinism and immunodeficiency. They suggested viral-induced CNS damage, but later reports of post-mortem examinations in FHL showed necrotising lymphohistiocytic infiltration [4]. Brismar et al. described four stages of CNS damage: (1) diffuse white matter changes and swelling (possible acute infection), (2) a quiescent period lasting many months, (3) acute white-matter swelling (possible re-infection), and finally (4) atrophy. Posterior fossa involvement dominated in their series. Cerebellar tonsils and the inferior aspect of the left cerebellar hemisphere were also involved in our case. The presence of calcifications suggests a somewhat later stage of the disease in

our patient. However, atrophy, a relatively constant late finding, was minimal initially and in the follow-up. Active parenchymal lesions in our case, as shown by contrast enhancement and some white-matter swelling, may have at least partly compensated for atrophy. Increasing calcifications during follow-up support a relatively more active stage of the disease. The clinical course, presenting with haemophagocytosis and later developing progressive neurological symptoms despite haematological remission, and neuroimaging findings are similar to those of other patients with GS [2, 6].

Henter et al. [8] evaluated post-mortem findings in 23 children with HS and correlated them with clinical, laboratory and, whenever present, radiological findings. They classified the clinical neurological findings into four stages: stage 0, no or non-specific neurologic abnormalities; stage I, non-specific signs, such as bulging fontanelle or hypotonicity; stage II, specific neurological signs such as neck stiffness, convulsions or pareses; stage III, severe neurological disease, such as a progressive psychomotor retardation or unconsciousness. Clinical staging correlated with neuropathological staging. Stage 0, no neuropathological abnormalities; stage I, focal infiltration of the meninges with lymphocytes and histiocytes/macrophages and with perivascular infiltrate; stage II, more prominent perivascular infiltrates and slight infiltration of the tissue in addition to more prominent meningeal infiltration, which sometimes involved the underlying cortex; stage III, diffuse parenchymal infiltration and multifocal tissue necrosis with prominent astrogliosis and relatively few foamy macrophages. Small calcifications may be seen. Necroses are mainly located in the white matter, but the adjacent cortex may be focally involved.

Although CSF findings do not always mirror the severity of the disease, high protein content and pleocytosis may be found in many patients, sometimes associated with subdural effusions [2, 6, 7]. Reduction of white matter volume leads to dilatation of the ventricular system, whereas cortical atrophy results in an increase of the subarachnoid space with widened sulci and narrowed gyri [4, 6]. A low CSF glucose content is also reported, despite absence of bacterial, viral and fungal infection, which is explained by rapid proliferation of lymphocytes and histiocytes or by alteration of the CSF–blood barrier to glucose [4].

In some patients, initial CT could be normal despite severe clinical signs of CNS involvement [8]. Later in the disease, CT reveals hypodense parenchymal lesions as well as more focal lesions with a contrast enhancement pattern mimicking abscess or metastases. The majority of these lesions disappear during chemotherapy or bone marrow transplantation.

The differential diagnosis of HS includes storage diseases, neurometabolic disorders, postinfectious or parainfectious encephalomyelitis, slow virus diseases such as subacute progressive panencephalitis, neurotoxic injury to immature brain from aggressive radiotherapy and/or chemotherapy (leucoencephalopathy and intracranial calcifications). For GD, the diagnosis is easier because of deficient pigmentation, provided the physician is familiar with this disease.

In conclusion, GD, although rare, should be included in the neuroimaging differential diagnosis for infants presenting with white/deep grey-matter demyelination or necrosis with calcifications and contrast enhancement. The optimum strategy for the treatment of FHL is to perform bone marrow transplantation as early as possible once complete systemic and neurological remission has been achieved.

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