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Case Report

Late-onset cerebral arteriopathy in a patient with incontinentia pigmenti

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Abstract

Background: Incontinentia pigmenti (IP) is an X-linked neurocutaneous disorder that can present with cerebral arteriopathy during early infancy. However, no previous reports have demonstrated arteriopathic manifestations during postinfantile childhood in patients with IP.

Patient description: We describe a case of IP in a 2-year-old girl who developed encephalopathic manifestations associated with influenza A infection. She presented diffuse magnetic resonance imaging abnormalities involving the cortices, subcortical white matter, corpus callosum, basal ganglia, and thalami, resembling the findings in early infantile cases reported in the previous literatures. Magnetic resonance angiography demonstrated attenuation of the cerebral arteries. Proinflammatory cytokines and chemokines were upregulated in the cerebrospinal fluid. Left hemiplegia remained following the remission of the arteriopathic manifestations. Genetic analyses revealed a novel type of mutation in the *IKBKG* gene.

Conclusion: Our findings indicate that patients with IP can develop destructive cerebral arteriopathy even after early infancy. The similarities in magnetic resonance imaging abnormalities between our patient and the previously reported infantile patients may be explained by the underlying immunologic pathophysiology of IP.

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Keywords: Incontinentia pigmenti; Cerebral arteriopathy; Influenza A virus; Cytokines; Chemokines; Encephalopathic manifestations

1. Introduction

Incontinentia pigmenti (IP) is an X-linked neurocutaneous syndrome characterized by skin lesions and disorders of various organs, including central nervous system

* Corresponding author at: Division of Child Neurology, Institute of Neurological Sciences, Faculty of Medicine, Tottori University, 86 Nishimachi, Yonago 683-8503, Japan. (CNS), retina, and teeth. The skin lesions are typically present during the neonatal period. IP results from a mutation at Xq28 encoding the *IKBKG* gene, involved in cell inflammation, immune responses, and cellular apoptosis [1,2].

Thirty to 50% of patients with IP have CNS involvement, including seizures, microcephaly, mental retardation, and hemiparesis [3,4]. Several reports have described early infantile encephalopathic manifestations

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with distinct magnetic resonance imaging (MRI) findings, and some authors have indicated vascular mechanisms as the cause of them [5–8]. However, the pathophysiology of the encephalopathic manifestations is not fully understood.

In the present report, we describe a case of a girl with IP who developed cerebral arteriopathy associated influenza A infection. The clinical course presented both arteriopathic and encephalopathic characteristics. We examined brain MRI findings, proinflammatory cytokines, and chemokines to elucidate the pathophysiology of the arteriopathy.

2. Patient description

The patient was born full-term following an uneventful pregnancy and delivery. At the age of three months, she was clinically diagnosed with IP based on the typical linear hypopigmentation, though she did not experience the vesicular stage as a newborn. She had no familial history of IP. Her neurological development until the age of 2 years was normal. At the age of 2 years and 3 months, she presented with 39 °C fever. After two days from the onset of the fever, her consciousness became severely impaired (the Glasgow Coma Scale was E1, V1, M3), without convulsions, for five hours. A scalp electroencephalogram (EEG) showed diffuse spike-andwave ictal activities in the right hemisphere, which resolved following intravenous infusion of midazolam and thiopental. Thereafter, she was referred to Tottori University Hospital.

Muscular tonus was weakened generally, particularly on the left side of the body, and deep tendon reflexes were absent in all extremities. Influenza A (H1N1) pdm09 virus was detected in her nasal mucosa by polymerase chain reaction (PCR). Laboratory tests, including PCR and antibody titers, did not reveal infection with any other virus. Blood tests revealed mild elevations in white blood cell count 10,200/µl and Creactive protein level (1.07 mg/dl). The autoantibodies associated with vasculitis were negative (Table 1). Cerebrospinal fluid (CSF) examination revealed mild increases in the initial pressure (20 cmH₂O), total protein (60 mg/dl), and immunoglobulin G (5.1 mg/dl). Anti-neuron antibodies in the serum and CSF were negative.

Brain MRI at the onset of the encephalopathic manifestation (day 0) revealed a slight enlargement of the right hemisphere and multiple punctate areas of restricted diffusion involving both hemispheres, but worse in the right one, including cortices, subcortical white matter, corpus callosum, thalami, basal ganglia, internal capsule, cerebral peduncles, and cerebellum (Fig. 1). The perfusion defects of the right hemisphere were detected on arterial spin labeling. Magnetic resonance angiography (MRA) showed moderate attenuation of the branches of the right middle (MCA) and posterior cerebral arteries (PCA).

Initially, she was diagnosed with acute hemorrhagic leukoencephalitis caused by influenza virus and treated with peramivir, fosphenytoin, edaravone, and two cycles of methylprednisolone pulse therapy (30 mg/day for 3 days), since the first cycle induced incomplete recovery of her consciousness (E4, V4, M5). She exhibited dysphasia after electrographic seizures ceased; dysphasia resolved by day 12 of illness. She completely regained consciousness by day 18 and could sit independently by day 21 of illness, although left hemiplegia remained. We performed brain MRI and MRA on day 1, day 6, day 14, and 4 months after the initial MRI (Fig. 1). MRA on day 1 revealed a recovered depiction of the MCA and PCA. Multiple punctate lesions gradually disappeared, though the relatively large lesions with hemorrhage became cavitary.

Screening for proinflammatory cytokines and chemokines in CSF on day 0 revealed marked upregulations, whereas those in serum did not (Table 2) [9].

At the age of 3 years and 10 months, she presented normal development with a developmental quotient of 113 in kinder infant development scale[®] (the median of the quotients is 100) and mild left spastic hemiplegia, although she could walk independently. Genetic sequencing using the Sanger's method identified a novel three-base deletion in the *IKBKG* gene, NM_003639.4: c. 976-978delAAG, asserted to be likely pathogenic according to the American College of Medical Genetics and Genomics standards and guidelines [10].

3. Discussion

Our patient with IP developed acute cerebral arteriopathy associated influenza A infection. She presented distinct arterial stenosis and hemorrhage on brain MRI and MRA during the acute phase. The arteriopathic or encephalopathic manifestations in IP has been reported on the neonatal or the early infantile patients in previous literatures [5–7]. To our knowledge, this may be the first report demonstrating the possibility of developing arteriopathy even in childhood for patients with IP.

One-third of patients with IP have CNS disorders [3,4]. Some previous cases showed stenotic changes of the multiple cerebral arteries on MRA in the acute phase of arteriopathy [6,7]. In the present case, the asymmetric and widespread punctate lesions with hemorrhage in brain MRI, and the branch attenuations of the cerebral arteries in MRA were similar to the image findings in the previous neonatal/early infantile cases. Although the onset was after the infantile period, the patterns of her MRI and MRA lesions indicated the arteriopathic mechanism similar to the previous cases.

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Blood test		Serum autoantibodies	CSF examination				
10,200	/µL	Anti-cardiolipin IgG antibody	≤ 8	U/mL	Cell count	1	/µL
11.2	g/dL	Anti-cardiolipin β2GPI antibody	≦1.2	U/mL	Mono	0	/µL
260	*10 ³ /μL	MPO-ANCA	<1.0	U/mL	Poly	1	/µL
231	mg/dL	PR3-ANCA	<1.0	U/mL	Cl	120	mmol/L
1.1	μg/mL	Antinuclear antibody	$\times 80$		Pro	60	mg/dL
45	U/L				Glu	74	mg/dL
16	U/L				Alb	36.2	mg/dL
281	U/L				IgG	5.1	mg/dL
72	mg/dL						
29	ng/mL						
1.07	mg/dL						
	10,200 11.2 260 231 1.1 45 16 281 72 29 1.07	10,200 /μL 11.2 g/dL 260 *10 ³ /μL 231 mg/dL 1.1 μg/mL 45 U/L 16 U/L 281 U/L 72 mg/dL 29 ng/mL 1.07 mg/dL	$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$	$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$	$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$	$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$	$\begin{array}{c c c c c c c c c c c c c c c c c c c $

Table 1 Examination findings

CSF, cerebrospinal fluid; WBC, white blood cell; Hb, hemoglobin; Plt, platelet; Fib, fibrinogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; TG, triglyceride; CRP, C-reactive protein; IgG, immunoglobulin G; GPI, glycoprotein; MPO, myeloperoxidase; ANCA, anti-neutrophil cytoplasmic antibody; PR3, proteinase 3; Mono, mononuclear cell; Poly, polynuclear cell; Cl, chlorine; Pro, protein; Glu, glucose; Alb, albumin.



Fig. 1. Serial brain magnetic resonance imaging and magnetic resonance angiography (MRA) findings after the onset. (A-C) Day 0. MRA showed moderate branch attenuation of the right middle (MCA) and posterior cerebral arteries (PCA) (arrowheads). Axial diffusion-weighted imaging (DWI) presented asymmetrically scattered punctate restricted diffusion in both hemispheres, involving the occipital cortices, subcortical white matter, corpus callosum, thalami, basal ganglia, and internal capsule. Arterial spin labeling imaging showed the perfusion defects of the right hemisphere. (D) Day 1. MRA revealed well-depicted branches of the right MCA and PCA. (E) Day 6. Susceptibility-weighted imaging showed petechial lesions in the same areas as DWI on day 0. (F) Four months after the onset (remote phase), small cavitary lesions were seen in the right occipital cortices, deep white matter, and corpus callosum on fluid attenuated inversion recovery imaging.

Tumor necrosis factor α and interleukin-6 (IL-6) significantly elevate at 1 month of age in a patient with *IKBKG* mutation, and decrease to normal levels with the resolution of the vesicular skin lesions [11]. Meanwhile, our patient presented with upregulation of various cytokines and chemokines including IL-6, 8, and 10 in CSF, suggestive of reaction to influenza A infection [12].

Influenza A virus infection can cause "influenzaassociated encephalopathy," which is an endemic

Table 2 Serum and CSF concentrations of cytokines and chemokines.

	BCA-1	Gro-a	IFN-γ	IL-1b	IL-6	IL-8	IL-10	IP-10	MCP-1	MIF	TNF-α
Serum (pg/mL)	20.68	88.68	<0.62	2.62	3.46	12.29	8.07	620.76 857.64*	25.16	1493.06	14.49
CSF (pg/mL)	0.84	427.23	12.39	49.44	89.34	123.91	55.51	837.04	1389.92	579.54	13.23

Serum and CSF levels of cytokines and chemokines were measured by Bio-Plex Suspension Array System (Bio-Rad).

*, Cytokine and chemokine values considered to be significantly elevated [9].

CSF, cerebrospinal fluid; BCA, B cell-attacking chemokine; Gro, growth related oncogene; IFN, interferon; IL, interleukin; IP, interferon gammainduced protein; MCP, monocyte chemoattractant protein; MIF, macrophage migration inhibitory factor; TNF, tumor necrosis factor.

encephalopathy in Japan and typically represents symmetrical lesions on cerebral cortices, white matter, or thalami [13], unlike the asymmetric and arteriopathic lesions in our patient. This encephalopathy may be associated with the genetic background of Japanese, and develops via the elevation of proinflammatory cytokines in CSF in childhood with a mean age of onset of 6.3 ± 3 . 4 years [12,13]. As the molecular pathogenesis in IP, the mutation of IKBKG results in a truncated nuclear factor kappa B (NF- κ B), which plays a role in protecting the integrity of brain endothelial cells and the blood-brain barrier [14]. Endothelial cell death can occur in response to a variety of potential stimuli, such as viral infections [15]. The proinflammatory cytokines in the CNS, upregulated following influenza A infection, might provide cerebral arteriopathy due to the increased susceptibility to inflammation of the endothelium caused by IKBKG mutation.

A large deletion from exon 4 to 10 in *IKBKG* gene is identified in 60–88% of patients with IP [1]. The skin lesions of our patient with IP were mild, namely she lacked the neonatal vesicular stage, presumably due to the in-frame shift of *IKBKG*. Abe et al. speculated that oxidative stress caused by the transition to the perinatal environment might result in neonatal brain injury in IP [5]. In the present case, since the susceptibility to inflammation might be mild due to the genotype, she was not affected by perinatal stimuli but rather by influenza A infection, which could cause the significant elevation of proinflammatory cytokines itself.

Given the findings supporting immune mechanisms as a part of the pathophysiology of cerebral arteriopathy in IP, immunosuppressive therapy may be a potential treatment strategy. MRI findings in the remote phase were milder in our patient than those in previously reported patients [5,6]. Immunosuppressive and neuroprotective therapy might prevent the exacerbation of arteriopathy, whereas steroid pulse therapy with heparinization should be carefully considered in patients with intracranial hemorrhage.

4. Conclusion

Patients with IP can develop cerebral arteriopathy accompanied by neurological sequelae even in child-

hood. Our findings indicate that the arteriopathy in IP might occur by the susceptibility of the endothelium to proinflammatory cytokines owing to the *IKBKG* mutation. Cytokines and chemokines can be substantially upregulated by viral infections, including influenza, resulting in the rarefaction of cerebral arteries in patients with IP.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethical approval

Written informed consent for the publication of this article was obtained from the patient's guardian.

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