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Case Report

Chronological dynamic changes in cortico-subcortical imbalance of cerebral blood flow in a boy with CAPOS syndrome

Aya Hashimoto [a], Ichiro Kuki [a,*], Masataka Fukuoka [a], Kiyohiro Kim [a], Takeshi Inoue [a], Megumi Nukui [a], Shin Okazaki [a], Hisashi Kawawaki [a], Yuji Nakamura [b], Shinji Saitoh [b]

[a] *Department of Pediatric Neurology, Osaka City General Hospital, Osaka, Japan*
[b] *Department of Pediatrics and Neonatology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan*

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Abstract

Background: Cerebellar ataxia, Areflexia, Pes cavus, Optic atrophy and Sensorineural hearing loss (CAPOS) syndrome is a known *ATP1A3*-related disorder, but little has been elucidated regarding its pathophysiology. We now report two new patients, a Japanese boy and his mother with a pathogenic mutation (c.2452G>A) in *ATP1A3,* who were diagnosed with CAPOS syndrome.

Methods: After febrile illnesses at 7 months of age, and again at 22 months of age, the boy had a reduced level of consciousness, truncal ataxia and eye movement-disorders. The patient's 32-year-old mother may have experienced an episode of acute encephalopathy in her childhood and sustained sensorineural hearing loss. In the present study, we demonstrated chronological dynamic changes in cerebral blood flow (CBF) in the son, using serial single-photon emission computed tomography (SPECT).

Results: The serial CBF-SPECT findings using statistical methods showed progressive hyperperfusion in the frontal lobes, basal ganglia and thalamus, and hypoperfusion in the occipital and temporal lobes during the acute and subacute phases. Thereafter, the dynamic changes of CBF improved in the chronic but hypoperfusion in thalamus appeared to the chronic phase.

Conclusion: The abnormal cortico-subcortical CBF may contribute to an acute encephalopathy-like condition in the acute stage of CAPOS syndrome. CAPOS syndrome is not often reported, and is possibly an under-recognized syndrome in clinically mild cases.

Keywords: Acute encephalopathy; Cerebellar ataxia; Cerebral blood flow; Sensorineural hearing loss; SPECT

1. Introduction

The *ATP1A3* gene on chromosome 19q13 encodes the Na+/K+ ATPase pump alpha3 subunit, which is expressed mainly in the central nervous system [1]. Currently, *ATP1A3* mutations are known to cause various types of overlapping neurological diseases, such as: Alternating Hemiplegia of Childhood (AHC); Rapid-onset Dystonia Parkinsonism (RDP); Early Infantile Epileptic

Abbreviations: CAPOS, Cerebellar ataxia, Areflexia, Pes cavus, Optic atrophy and Sensorineural hearing loss; CBF, cerebral blood flow; SPECT, single-photon emission computed tomography; CSF, cerebrospinal fluid; EEG, electroencephalography; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy

* Corresponding author at: Department of Pediatric Neurology, Osaka City General Hospital, 2-13-22 Miyakojimahondori, Miyakojima-ku, Osaka 534-0021, Japan.
E-mail address: i-kuki@med.osakacity-hp.or.jp (I. Kuki).

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Encephalopathy; Relapsing Encephalopathy with Cerebellar Ataxia (RECA); and Cerebellar ataxia, Areflexia, Pes cavus, Optic atrophy and Sensorineural hearing loss (CAPOS) syndrome [2,3].

In 1996, CAPOS syndrome was first reported by Nicolaides et al. [4]. In 2014, Demos et al. described an additional seven patients from two families and also reported that heterozygous c.2452G>A mutations in *ATP1A3* cause CAPOS syndrome [1]. Up to the present day, there have been over thirty case reports on this syndrome [1,4–8], but little has been elucidated regarding the pathophysiology of CAPOS syndrome. Moreover, functional neuroimaging has not been reported in patients with CAPOS syndrome.

In this report, a Japanese boy and his mother with CAPOS syndrome are described, along with the sequential single-photon emission computed tomography (SPECT) imaging that was conducted on the boy.

2. Case report

The patient is a two-year-old boy. He was born normally, at term, and achieved normal developmental milestones. After a febrile illness when he was 7 months old, he displayed a reduced level of consciousness, truncal ataxia and an eye movement disorder. He recovered, without any prognostic symptoms, after the steroid pulse therapy and high-dose intravenous immunoglobulin therapy which are the standard treatments for acute encephalitis. He was able to stand up on his own and speak some meaningful words by the time he was 18 months old. His two older siblings were healthy. His 32-year-old mother experienced an episode of acute encephalopathy in her childhood. She had sustained sensorineural hearing loss from that time, but did not have cerebellar ataxia, pes cavus or optic atrophy. There was no other relevant family history.

At 22 months of age, the patient again experienced a febrile illness. Three days after the fever was detected, he showed symptoms of aphasia and was unable to remain sitting upright (day1). On day 7, his level of consciousness was disturbed, and fixation, pursuit and tracking eye-movements were all impaired. The patient could not hold his head up, and he had truncal ataxia, hypotonia, absence of deep tendon, abdominal, and Babinski's reflexes. Blood test including metabolic investigation, electroencephalography (EEG), and an examination of his cerebrospinal fluid (CSF) showed no abnormality. A head computed tomography scan and magnetic resonance imaging (MRI) on day 7 showed no abnormalities. There were no noteworthy findings on magnetic resonance spectroscopy (MRS) on day 28. Peripheral conduction velocity was reduced in the median motor nerve, and sural sensory nerve conduction could not be detected. ^{123}I-iomazenil SPECT on day 40 showed no abnormal findings.

We obtained written informed consent from the parents, and performed serial SPECT imaging of cerebral blood flow (CBF) using ethyl cysteinate dimer in the three phases; acute phase on day 21, subacute phase on day 49 and chronic phase on day 96. By the visual inspection of the original images, hyperperfusion in the basal ganglia, and hypoperfusion in the cerebral cortex in the acute phase. In the subacute phase, increase of uptake were shown in the frontal lobes, basal ganglia and thalamus. Thereafter, the dynamic changes of CBF improved in the chronic phase. To provide objectively interpretation of SPECT, we analyzed the SPECT data using easy Z-score imaging system (eZIS), which is a computer-assisted statistical analysis, based on the comparison with normal database [9]. Moreover, we also evaluated the serial data using subtraction ictal single-photon emission CT coregistered to MRI (SISCOM) analysis (Fig. 1) [10]. The result of eZIS and SISCOM showed progressive hyperperfusion in the frontal lobes, basal ganglia and thalamus, and hypoperfusion in the occipital and temporal lobes during the acute and subacute phases. Thereafter, the dynamic changes of CBF improved in the chronic but hypoperfusion in thalamus appeared to the chronic phase. No abnormal findings were indicated in the cerebellum in any phases.

He gradually recovered, and developed the ability to speak two-word sentences and walk unstably by himself 6 months after the appearance of symptoms. At present, His visual behavior and ophthalmic test is normal, but his auditory steady state response is mildly abnormal.

We suspected RECA or another ATP1A3-related disease because of the patient's repeated symptoms of acute encephalopathy and cerebellar ataxia. We performed a next-generation sequencing using Trusight One Panel (Illumina) which captures exons of 4813 genes and identified a heterozygous c.2452G>A (p.Glu818Lys) mutation in the *ATP1A3* gene. We performed Sanger sequencing and confirmed the variant in the patient and his mother. We obtained approval of this study from the institutional ethical committee and informed consent for publication of clinical data and gene analysis from the family.

3. Discussion

In both a 22-month-old boy, who had twice had fever-induced encephalopathy with reduced consciousness, truncal ataxia and an eye-movement disorder, and in his mother, we identified a heterozygous c.2452G>A mutation in the *ATP1A3* gene. This mutation is known to cause CAPOS syndrome [1]. We have demonstrated the chronological dynamic changes of CBF on serial SPECT after the encephalopathy.

Table 1 summarizes the findings of functional neuroimaging in previously reported cases with identified *ATP1A3* mutations compared with the presented cases.

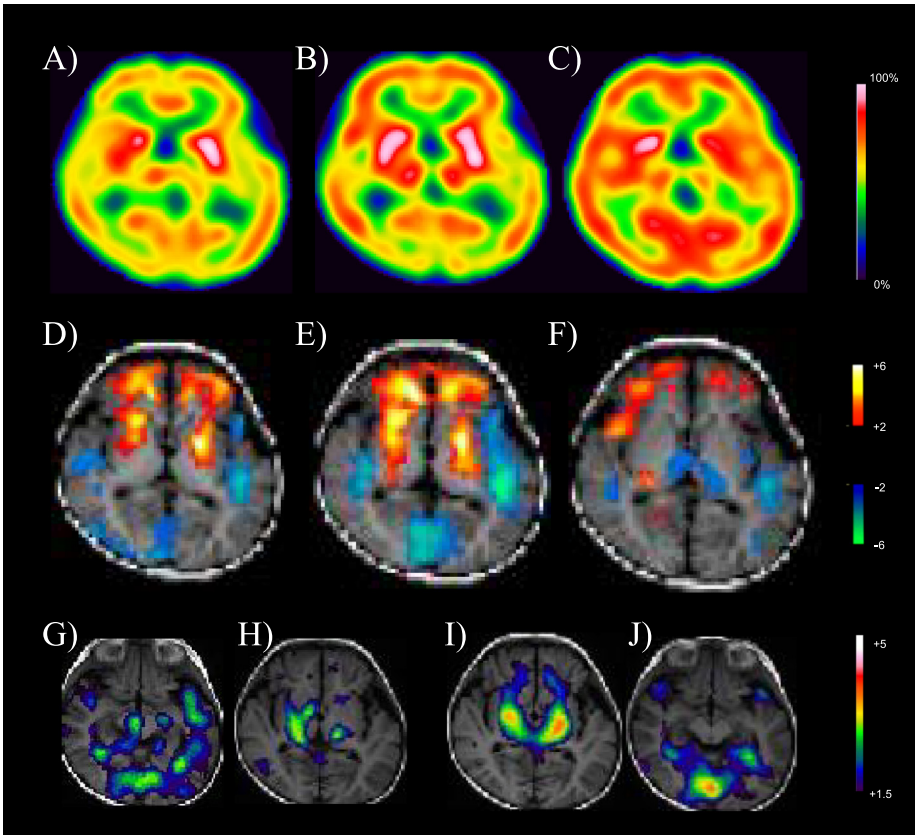

Fig. 1. Serial SPECT imaging of cerebral blood flow (CBF). Original images of CBF, which are performed in the acute phase (A), in the subacute phase (B) and in the chronic phase (C), are shown. The statistical images (D–F) show eZIS data. The images showing abnormal CBF distribution are noted in the acute phase (D), in the subacute phase (E) and in the chronic phase (F). The Statistical images (G–J) show SISCOM data. The image (G) reveals the subtraction of the data in the subacute phase from that in acute phase; in the acute phase from in the subacute phase (H), in the subacute phase from chronic phase (I), in the chronic phase from subacute phase (J), respectively. These statistical images show progressive hyperperfusion in the frontal lobes, basal ganglia and thalamus, and hypoperfusion in the occipital and temporal lobes during the acute and subacute phases. The dynamic abnormalities in CBF improved, but hypoperfusion in the thalamus appeared in the chronic phase.

No CBF evaluations have been reported to-date in patients with CAPOS syndrome. Some previous studies showed functional neuroimaging in patients with *ATP1A3*-related disorders. Striatal ^{123}I-ioflupane uptake, which is related to striatal dopamine transporters, showed values just within the normal range, and a ^{99}mTc-hexamethylpropylene amine oxime scan was normal, in a sporadic case of RDP with a novel mutation in the *ATP1A3* gene [11,12]. CBF-SPECT detected laterality in cerebral blood perfusion on the acute phase in an atypical form AHC, which might be considered RECA clinically and genetically [13]. Moreover, interictal fluorodeoxyglucose-positron emission tomography in AHC patients revealed low glucose metabolism in the frontal lobes, with some laterality, and in the ipsilateral putamen and cerebellum, although no description about *ATP1A3* mutations were noted in the report [14]. No laterality of CBF in all phases was shown in the presented case, therefore the pathophysiology of CAPOS syndrome may differ from those of other ATP1A3-related disorders in terms of CBF distribution during neurological attacks.

Let us now consider the pathomechanism of CAPOS syndrome. The decreased level of consciousness in this CAPOS syndrome case is, in some aspects, similar to that in patients with viral-associated acute encephalopathy or autoimmune encephalitis. In those diseases, abnormal background activity in EEG, characteristic lesions with abnormal intensity in MRI, and/or cell or protein elevation in CSF are usually seen during the acute phase. However, those abnormalities were not present in our patient. In addition to the normal findings on MRI, EEG, and CSF, ^{123}I-iomazenil SPECT and MRS were normal. Therefore, the pathomechanism of CAPOS syndrome might not involve inflammatory change, ischemia, demyelination and dysfunction of inhibitory neurons, but rather dynamic changes in cortico-subcortical CBF, as demonstrated in this patient's serial SPECT evaluations.

It is worth reiterating that the boy's mother was deemed to have an early-childhood history of acute encephalopathic ataxia, but she has only mild symptoms of sensorineural hearing loss. Table 2 summarizes the clinical features in previously reported CAPOS cases

Table 1
Functional neuroimaging of patients with ATP1A3 mutations.

Source: Author, year	Present case	Zanotti-Fregonara et al. (2008)		Svetel et al. (2010)	Kanemasa et al. (2016)
Clinical classification	CAPOS	RDP		RDP	An atypical form AHC (RECA)
Mutation in ATP1A3	c.2452G>A, p.E818K	c.2767 G>A, p.D923N		c2051C>T, p.S684F	c.2266C>T, p.R756C
Age at reported evaluation	1-year-old	40-year-old woman		32-year-old woman	7-year-old boy
Functional neuroimaging	99mTc-ECD-SPECT	[123I]-FP-CIT-SPECT	99mTc-HMPAO-SPECT	[123I]-FP-CIT-SPECT	99mTc-ECD-SPECT
Date of evaluation	21nd, 49nd and 96 day of admission	NA	NA	NA	22nd day of admission
Findings of functional neuroimaging	Progressive hyperperfusion in the frontal lobes, basal ganglia and thalamus, and hypoperfusion in the occipital and temporal lobes during the acute and subacute phases Hypoperfusion in thalamus in the chronic phase	Normal and symmetric uptake in both striata	Homogeneous cortical and sub-cortical perfusion	Normal and symmetric uptake in both striata	Decreased perfusion area in the left hemisphere and the right striatum

CAPOS: cerebellar ataxia, areflexia, pes cavus, optic atrophy and sensorineural hearing loss, AHC: alternating hemiplegia of childhood, RDP: rapid-onset dystonia-parkinsonism, NA: not applicable.

compared with the presented cases. Prior to the report by Chang et al. in 2018 [6], all reported cases of CAPOS syndrome had cerebellar ataxia and areflexia, including the case without an acute episode [3–8]. Recently Han et al. mentioned a 31-year-old female patient with sensorineural hearing loss without an attack of ataxia [7]. Unlike that in most reported patients, the mother's hearing loss in the present case was slight, despite the acute history. Thus, patients with only optic atrophy or sensorineural hearing loss may, in fact, have the c2453G>A mutation in *ATP1A3*. These findings suggest that some such mild cases may not be recognized as CAPOS syndrome. If these CAPOS cases can, in fact, be recognized, then doctors can predict the symptoms that are likely to occur in the future, and intervene early with language support in cases of sensorineural hearing loss, or rehabilitation for pes cavus, etc. At the same time, by increasing the number of patients who are diagnosed with CAPOS syndrome, additional clinical data can be collected, leading to the elucidation of the pathophysiology and establishment of therapeutics for this syndrome.

Table 2
Summary of clinical features in previously reported CAPOS cases compared with the presented cases.

	Reported cases	The son	The mother
Age of onset	7 month–7 year (median. 2 year)	7 month	2 year
Age of last episode	9 month–37 year (median. 4 year)	1 year 6 month	2 year
Number of acute episodes	0–6 times (median. 2)	2 times	1 time
Acute symptoms	29 of 32 cases (90.0%)		
Cerebellar ataxia	29 of 29 cases (100.0%)	+	NA
Consciousness disturbance	16 of 29 cases (55.2%)	+	NA
Hypotonia	18 of 29 cases (62.0%)	+	NA
Hemi-/para-/tetraplegia	5 of 29 cases (17.2%)	+	NA
Abnormal eye movement	11 of 29 cases (37.9%)	+	NA
Dysphagia/anarthria	6 of 29 cases (20.7%)	+	NA
Most recent examination			
Cerebellar ataxia	30 of 32 cases (93.8%)	+	–
Areflexia	31 of 32 cases (96.9%)	+	NA
Pes cavaus	11 of 32 cases (34.4%)	–	–
Optic atrophy	29 of 32 cases (90.6%)	–	–
Sensorineural hearing loss	31 of 32 cases (96.9%)	+	+
Full CAPOS syndrome	11 of 32 cases (34.4%)	–	–

CAPOS: Cerebellar ataxia, Areflexia, Pes cavus, Optic atrophy and Sensorineural hearing loss, NA: not applicable.

Several limitations of our study need to be considered. First, we could not use a standard database of CBF-SPECT for infants. We were, however, able to investigate the serial changes in the Z-score, based on the adult database. SISCOM could also be applied even in pediatric patients in general. Second, unfortunately we do not know the details of the mother's condition when she experienced the episode of acute encephalopathy in her childhood. Some family cases of CAPOS syndrome have been reported [4–6]. The clinical features were multifarious and different in each case in each family. Both penetrance and expressivity for the ATP1A3 gene are yet to be clarified so further studies are required.

In conclusion, we conducted serial SPECT imaging of CBF in patients with CAPOS syndrome. Chronological dynamic changes in cortico-subcortical imbalance of CBF could lead to clinical features of characteristic encephalopathy in CAPOS syndrome. To further elucidate the pathomechanism of acute clinical features in CAPOS, more studies are needed.

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6. Contributors' statement

Aya Hashimoto, Ichiro Kuki and Masataka Fukuoka conceptualized the report, wrote the manuscript, and were responsible for all stages of the report. Kiyohiro Kim, Takeshi Inoue and Megumi Nukui were responsible for collection of the data. Shin Okazaki and Hisashi Kawawaki critically revised the manuscript for important intellectual content and helped to draft the manuscript. Yuji Nakamura and Shinji Saito performed the gene analysis and its interpretation. All authors read and approved the final manuscript.

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