

TABLE.
Previously Published Cases of VPA-induced Fanconi Syndrome

Patient number	Age (y)/ Sex	Clinical remarks	Severe disability	Tube feeding	VPA duration	VPA blood level, µg/mL	Other AEDs	Time to recovery	Opportunity that disclosed FS	Reference
1	27/F	Epilepsy	No	No	5 y	136	None	1 wk	Fatigue, confusion	1
2	6/M	Cerebral palsy	Yes	Yes	5 1/2 y	81.4	PHT, CLB	6 mo	Edema	2
3	15/M	Cerebral palsy	Yes	Yes	14 1/2 y	75	CBZ, CLB	3 mo	Laboratory study	2
4	10/F	Cerebral palsy, lissencephaly	Yes	-	16 mo	69.8	PB, GBP	5 mo	Laboratory study	2
5	9/M	Anoxic encephalopathy	Yes	Yes	Several years	49.3	PB, DZP	4 mo	Laboratory study	2
6	4/F	Perinatal anoxic encephalopathy	Yes	Yes	3 1/2 y	60.2	CBZ	4 mo	Laboratory study	2
7	8/M	West syndrome	Yes	-	7 y	64	CZP, TPM	2 mo	Laboratory study	3
8	6/F	Cerebral retardation	Yes	-	2 1/2 y	-	CLB	14 mo	Weakness	3
9	12/M	Petit mal epilepsy	No	No	19 mo	-	PB	6 mo	abdominal pain, myopathy-like	4
10	10/M	Severe and global neurologic impairment	Yes	-	10 mo	-	PHT, lorazepam	3 mo	Hypertension	5
11	10/M	Epilepsy	No	No	18 mo	-	None	Renal failure	Laboratory study	6
12	9.5/M	Birth asphyxia	-	-	8 y	-	CZP, CBZ	4 mo	Fracture	7
13	19/M	Cerebral palsy	-	-	-	-	PB	-	Fracture	7
14	15/M	Near-drowning	Yes	Yes	13 y	89.2	None	3 mo	Laboratory study	8
15	6/F	Neonatal asphyxia	Yes	Yes	6 y	73.9	CLB	2 mo	Laboratory study	8
16	6/F	Neonatal asphyxia	Yes	Yes	6 y	119.8	None	2 mo	Laboratory study	8
17	2/F	Early infantile epileptic encephalopathy	Yes	Yes	12 mo	94.7	ZNS, CLB	3 mo	Fever of unknown origin	8
18	4/M	Pachygyria	Yes	Yes	4 y	62	None	18 mo	Laboratory study	8
19	8/F	Neonatal asphyxia	Yes	Yes	8 y	95	None	2 mo	Laboratory study	8
20	13/F	Neonatal asphyxia	Yes	Yes	7 y	141	None	12 mo	Fever of unknown origin	8
21	8/F	Chromosome abnormality	Yes	Yes	6 y	98.96	-	2 mo	fever	9
22	4/M	West syndrome	Yes	Yes	3 y	40	PB, ZNS	9 mo	Laboratory study	10
23	10/M	Partial epilepsy	No	No	12 mo	21	None	18 mo	Laboratory study	10
24	7/M	Lissencephaly	Yes	Yes	7 y	129.7	PB, CZP	2 mo	Edema	10
25	7/F	Near-drowning	Yes	Yes	2 y	57.2	CBZ	15 mo	Laboratory study	10
26	9/F	Hypoxic ischemic encephalopathy	Yes	Yes	8 y	81.6	-	4 mo	Laboratory study	11
27	22/M	West syndrome	Yes	Yes	21 y	-	-	1 mo	Laboratory study	12
28	-	Encephalopathy sequelae	Yes	Yes	2 y	-	ZNS	3 mo	Fracture	13
29	-	Encephalopathy sequelae	Yes	Yes	4 y	-	ZNS	3 mo	Fracture	13
30	-	Chromosome abnormality	Yes	Yes	4 y	-	CBZ, PHT	Proteinuria	Laboratory study	13
31	-	Epilepsy	Yes	Yes	3 y	-	KBr	1 mo	Laboratory study	13
32	-	Brain malformation	Yes	Yes	9 y	-	PB	3 mo	Fracture	13
33	-	Cerebral palsy	Yes	Yes	4 y	-	ZNS	6 mo	Tachypnea	13
34	-	Cerebral palsy	Yes	Yes	8 y	-	none	9 mo	Fracture	13
35	-	Cerebral palsy	Yes	Yes	3 y	-	CLB, ZNS, PB, KBr	9 mo	Fracture	13
36	-	Neurodegenerative disease	Yes	Yes	3 y	-	CZP, PB, DZP	6 mo	Fracture	13
37	-	Cerebral palsy	Yes	Yes	3 y	-	ZNS, PB	2 mo	Fracture	13
38	-	Encephalopathy sequelae	Yes	Yes	3 mo	-	ZNS, PB	6 mo	Tachypnea	13
39	-	Neurocutaneous syndrome	Yes	Yes	12 mo	-	ZNS	6 mo	Tachypnea	13
40	4/M	Congenital myopathy	Yes	Yes	-	-	None	3 mo	Lower respiratory tract infection	14
41	8/F	West syndrome	Yes	Yes	6 y	74.2	PHT, PB, CZP, ZNS	5 mo	Pneumonia	15
42	2/F	Chromosome abnormality	Yes	Yes	2 y	122.7	CBZ, CLB	2 mo	Gastroenteritis	15
43	3/M	Epilepsy	Yes	Yes	3 y	65.6	ZNS, GBP	1 mo	Upper respiratory infection	15
44	8/F	Myoclonic epilepsy	Yes	Yes	7 y	-	CLB	12 mo	Fracture	16
45	14/M	Epilepsy	No	No	2 y	-	-	6 mo	Weakness	17
46	10/F	Partial deletion of chromosome 4p	Yes	Yes	9 y	-	TPM	12 mo	Laboratory study	18
47	2/F	Type 2 Gaucher disease	Yes	Yes	2 y	80.2	CLB, TPM	2 mo	Fracture	19
48	11/M	Cerebral palsy, epilepsy	Yes	-	11 y	-	PB, ZNS CLB, KBr	A couple of weeks	Respiratory illness	20
49	32/F	Neonatal asphyxia	Yes	-	-	-	-	-	Pneumonia	20

Abbreviations:

AEDs = Antiepileptic drugs

CBZ = Carbamazepine

CLB = Clobazam

CZP = Clonazepam

DZP = Diazepam

FS = Fanconi syndrome

GBP = Gabapentin

KBr = Potassium bromide

PB = Phenobarbital

PHT = Phenytoin

TPM = Topiramate

VPA = Valproate

ZNS = Zonisamide

Severe disability means bedridden or wheelchair-bound.

uncoupling or “loose coupling” of oxidative phosphorylation in the mitochondria, which may cause fever and weight loss because of hypermetabolism, as found in Luft’s disease.²¹ However, valproate is not known to have an uncoupling effect. Our patient had a cytochrome oxidase deficiency, which itself could cause Fanconi syndrome. However, the fact that Fanconi syndrome resolved with VPA withdrawal indicated that the mitochondrial disease was not a direct cause of Fanconi syndrome in the present patient.

In conclusion, VPA-induced Fanconi syndrome should be considered when patients taking VPA develop fever of unknown origin. Furthermore, individuals taking VPA, especially those who are severely disabled and tube-fed, should be given carnitine supplementation and be periodically screened for Fanconi syndrome.

This study was supported in part by a grant from the Research Program of Innovative Cell Biology by Innovative Technology (Cell Innovation), a Grant-in-Aid for the Development of New Technology from The Promotion and Mutual Aid Corporation for Private Schools of Japan from MEXT, and Grants-in-Aid for the Research on Intractable Diseases (Mitochondrial Disease) from the Ministry of Health, Labour and Welfare (MHLW) of Japan to A. O. and K. M. Dr Murayama was supported by the Kawano Masanori Memorial Public Interest Incorporated Foundation for Promotion of Pediatrics.

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本報告書は、厚生労働省の厚生労働科学研究委託事業による委託業務として、千葉県がんセンター病院長（主任研究者職・氏名 主任医長・村山圭）が実施した平成26年度「ミトコンドリア病診療の質を高める、レジストリシステムの構築、診断基準・診療ガイドラインの策定および診断システムの整備を行う臨床研究」の成果を取りまとめたものです。

