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1 **Hematopoietic stem cell transplantation for cytidine triphosphate synthase 1 (CTPS1) deficiency**

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18 **Capsule Summary**

19 CTPS1 deficiency causes early onset herpes virus infections particularly with VZV and EBV and there is a high risk of developing
20 lymphoma. We report eleven patients treated by hematopoietic stem cell transplantation, eight of whom survived with resolution of
21 symptoms.

22

23 **Key word:** CTPS1, primary immune deficiency, hematopoietic stem cell transplantation, EBV, lymphoma

24

25 **Word Count: 944**

26 ***To the Editor,***

27 Cytidine triphosphate (CTP) synthase 1 is responsible for the catalytic conversion of uridine triphosphate (UTP) to CTP in
28 lymphocytes.¹ This reaction is important for the biosynthesis of nucleic acids, playing a key role in lymphocyte function and
29 turnover¹⁻². Lack of this enzyme due to mutation in *CTPS* gene is associated with impaired capacity of activated T and B-
30 lymphocytes to proliferate in response to antigen-induced activation. Patients with this mutation all have ancestors from the North
31 West of England¹ and present in the first decade of life with severe acute and chronic herpes virus infections and recurrent
32 infections with encapsulated bacteria. There is a high risk of EBV-driven lymphoma.¹ This is a potentially life-threatening primary
33 immune deficiency (PID) and long-term survival has not been reported.

34 We report on 11 patients with *CTPS1* mutations who underwent hematopoietic stem cell transplant (HSCT) at three UK
35 centres (London, Manchester and Newcastle). The molecular diagnosis was made pre-HSCT in six patients and retrospectively in
36 five patients who had undergone HSCT for previously undiagnosed life-threatening PID. All patients had the same homozygous
37 NM_001905.3: c.1692-1G>C mutation (rs145092287) mutation and all the parents were heterozygous carriers. This mutation is
38 known to lead to an abnormal transcript lacking exon 18 and complete lack of protein expression.¹ Six patients had an affected
39 sibling. Patient 1 had 2 affected siblings who died of infection and hemophagocytic lymphohistiocytosis (HLH) in early childhood
40 and patient 2 also had a sibling who died of overwhelming VZV and EBV infections before diagnosis. Pre-transplant features are
41 summarized in Table 1. Systemic viral infections were seen in all patients, with acute and chronic EBV infections in nine patients,

42 four suffering from EBV-driven lymphoproliferative disease (LPD) (two CNS and one lung) and one with EBV-driven HLH. Four
43 patients had severe chickenpox. Five patients presented with chronic diarrhea.

44 Four patients with EBV-driven LPD received rituximab and three EBV-specific cytotoxic T-lymphocytes (CTLs) (two pre-
45 transplant and one post-transplant). The age of the patients at transplant ranged from 15 months to 17 years. The source of stem
46 cells was peripheral blood (PB) in seven patients, bone marrow (BM) in three and cord blood (CB) in one. Eight received matched
47 (10/10) donor stem cells, two had 1/10 mismatches and one received a haploidentical 6/10 transplant from his father as there were
48 no suitable matched donor (Table 2). All but one received conditioning with fludarabine in combination with treosulfan (n=3),
49 melphalan (n=4), treosulfan and thiotepa (n=1, the non-reduced intensity conditioning (RIC) protocol) or low dose busulfan (n=2)³,
50 one received treosulfan and cyclophosphamide. All but one patient received serotherapy with alemtuzumab (n=8) or anti T cell
51 globulin (ATG) (n=2). CD34⁺ cell dose ranged from 0.4 - 16.1 x 10⁶/kg. Neutrophil engraftment ($\geq 0.5 \times 10^9$ /L) occurred between day
52 11- 23 post-transplant. Ten had 100% CD3 donor engraftment and one had 76% in last follow up.

53 Eight patients are alive with post-HSCT follow-up of 8 months to 22 years. All surviving patients have discontinued
54 immunosuppression and six are off immunoglobulin replacement therapy. Patient 4 died 76 days post-HSCT following EBV CNS
55 reactivation leading to obstructive hydrocephalus. She was treated with external ventricular drainage and three doses of 2×10^6
56 EBV-CTLs but died of multi-organ failure ⁴. Patient 7 developed intractable gut inflammation due to a combination of adenovirus
57 and CMV colitis and chronic graft versus host disease (cGvHD) and died at day +290 despite treatment with ganciclovir and

58 cidofovir for the viral infections and corticosteroids, ciclosporin, tacrolimus and infliximab as anti-inflammatory drugs. Patient 8
59 developed mild acute skin GvHD post-transplant, but later suffered from intractable chronic skin GvHD (but no gut or liver disease)
60 unresponsive to corticosteroids and extracorporeal photophoresis. Twelve months post-transplantation he developed a tremor and
61 altered mental state progressing to coma and died 15 months post-transplant. Brain biopsy and magnetic resonance (MR) scan
62 performed prior to death were indicative of progressive multifocal leukoencephalopathy (PML), although no JC, BK or astrovirus
63 were isolated from cerebrospinal fluid (CSF) or brain tissue.

64 CTPS1 deficiency is a serious life-limiting immunodeficiency with a high risk of death from VZV and EBV in the first decade
65 of life. Seven (41%) of 17 patients worldwide with CTPS1 deficiency have died, three post and four prior to HSCT (one from
66 fulminant VZV and the other three from fulminant EBV LPD). These deaths were prior to clinical availability of rituximab. However,
67 mild clinical phenotype has previously been described ⁵. HSCT can be curative but is not without potential risks and complications.
68 Kucuk et al also reported two siblings with this mutation who had successful transplantation ⁶. The current report is the largest
69 series of children with CTPS1 deficiency who have undergone HSCT. The overall survival post-HSCT in this series was 72% which
70 is slightly lower than seen after HSCT for other combined PIDs⁷. Pre-transplantation, extra-nodal EBV-driven LPD of the brain and
71 lung as well as fulminant VZV pneumonitis requiring ventilation in intensive care are major risks. The post-transplantation course
72 can be challenging to even the specialist centres because of re-activation of EBV and other herpes viruses, particularly in the brain
73 and gastrointestinal tract, but also because of the risk of unusually severe skin and gut cGvHD, the latter which may be partly

74 fuelled by ongoing underlying low grade chronic viral infection. Both patients that developed fatal GvHD had transplants from 9/10
75 matched unrelated donors. Viral reactivation can be observed prior to donor T-lymphocyte engraftment post-transplant and perhaps
76 virus-specific CTLs may be helpful in some of these patients. There is no doubt that HSCT can be curative in this condition and we
77 recommend early transplantation before the onset of end-organ damage and for patients without fully matching family or unrelated
78 donors, the consideration of ex-vivo T-cell depletion strategies.

79 The authors confirm there is no conflict of interest.

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104 **References**

- 105 1. Martin E, Palmic N, Sanquer S, Lenoir C, Hauck F, Mongellaz C et al. CTP synthase 1 deficiency in humans reveals its
106 central role in lymphocyte proliferation. *Nature* 2014; 510:288-292.
- 107 2. Wynn RF, Arkwright PD, Haque T, Gharib M, Wilkie G, Morton-Jones M et al. Treatment of Epstein-Barr-virus-associated
108 primary CNS B-cell lymphoma with allogeneic T-cell immunotherapy and stem-cell transplantation. *Lancet Oncol* 2005;
109 6:344-46.
- 110 3. Güngör T, Teira P, Slatter M, Stussi G, Stepensky P, Moshous D et al. Reduced-intensity conditioning and HLA-matched
111 haemopoietic stem-cell transplantation in patients with chronic granulomatous disease: a prospective multicentre study.
112 *Lancet* 2014; 383:436-48.
- 113 4. Naik S, Nicholas S, Martinez C, Leen A, Hanley P, Gottschalk S et al. Adoptive Immunotherapy for Primary
114 Immunodeficiency Disorders with Virus-Specific Cytotoxic T-lymphocytes. *J Allergy Clin Immunol* 2016; 137: 1498-1505.

- 115 5. Trück J, Kelly DF, Taylor JM, Kienzler A, Lester T, Seller A et al. Variable phenotype and discrete alterations of immune
116 phenotypes in CTP synthase 1 deficiency: Report of 2 siblings. J Allergy Clin Immunol, 2016; Volume 138, Issue 6, Pages
117 1722–1725.
- 118 6. Kucuk ZY, Zhang K, Filipovich L, Blessing J. CTP Synthase 1 Deficiency in Successfully Transplanted Siblings with
119 Combined Immune Deficiency and Chronic Active EBV Infection. J Clin Immunol. 2016 Nov; 36(8):750-753.
- 120 7. Dvorak CC, Cowan MJ. Hematopoietic stem cell transplantation for primary immunodeficiency disease. Bone Marrow
121 Transplant. 2008 Jan; 41(2):119-26.

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Table 1 Patient characteristics

Patient	Sex	Clinical history									Family History	lymphocytes subset (x10^9/L)	Immunoglobulin Normal range (g/L) IgG(3.7-15.8) IgA(0.3-1.3) IgM(0.5-2.2)	Age at presentation
		<u>SPI</u>	<u>EBV-LPD</u>	<u>S VZV</u>	<u>Chronic Diarrhoea</u>	<u>HLH</u>	<u>Viral viremia</u>	<u>IPI</u>	<u>lymphoma</u>					
Pt1	M	Y	N	N	Y (HHV6)	N	N	N	N	Y	CD19 0.3, CD3 2.2, CD4 0.9, CD8 1.2, NK 0.49	IgG 19.1, IgA 0.5, IgM 0.84	4 months	
Pt2	F	N	N	Y	N	N	Y (EBV)	N	N	Y	CD19 1.1, CD3 1.9, CD4 1.4, CD8 0.37, NK 0.21	IgG 5.5, IgA 2.5, IgM 0.5	17 months	
Pt3	M	Y (ADV)	Y	N	Y (Norovirus)	N	Y (EBV)	N	Y (CNS)	N	^CD19 0, CD3 0.47, CD4 0.43, CD8 0.02, NK 0.03	IgG 4.8, IgA 4.4, IgM 0.8	5 months	
Pt4	F	N	Y	Y	N	Y	N	N	N	N	^CD19 0.01, CD3 0.52, CD4 0.25, CD8 0.25, NK 0.03	IgG 7, IgA 0.46, IgM 0.39	6 years	
*Pt5	F	Y (Hinf)	Y (CNS)	Y	N	N	N	N	N	Y	^CD19 0.13, CD3 0.46, CD4 0.28, CD8 0.18, NK 0.02	IgG 10.9, IgA 2.01, IgM 0.59	1 month	
*Pt6	M	Y (Hinf)	N	N	N	N	Y (EBV)	N	N	Y	CD19 0.17, CD3 0.99, CD4 0.57, CD8 0.48, NK 0.12	IgG 6.41, IgA 0.42, IgM 0.47	3 years	
**Pt7	F	Y	N	N	Y	N	Y (EBV)	N	N	Y	CD19 1.01, CD3	IgG 24.7, IgA 0.6,	7 months	

		(EBV)										4.39, CD4 1.41, CD8 2.58	IgM 0.84	
**Pt8	M	Y (EBV)	N	N	Y		N	Y (EBV)	N	N	Y	CD19 0.65, CD3 1.68, CD4 0.83, CD8 0.78, NK 0.05	IgG 12.4, IgA 0.66, IgM 0.12	14 months
Pt9	M	Y	N	N	Y		N	Y (EBV)	Y	N	N	CD19 0.25, CD3 1.8, CD4 1.1, CD8 0.62, NK 0.15	IgG 5.34, IgA 1.01, IgM 0.62	2 months
Pt10	F	Y	N	Y	N		N	N	N	N	N	CD19 0.4, CD3 3.7, CD4 1.3, CD8 2.3, NK 0.09	IgG 16.70, IgA 0.45, IgM 0.24	7 years
Pt11	M	Y	Y (LUNG)	Y	N		N	N	N	N	N	CD19 0.3, CD3 2.8, CD4 1.7, CD8 0.9, NK 0.2	IgG 16.5, IgA 1.45, IgM 1.10	2 years

Pt: Patient; M: Male; F: Female; LPD: Lymphoproliferative disease; EBV: Epstein Bar virus; VZV: varicella zoster virus; ADV: Adenovirus; HHV6: Human Herpes Virus 6; Hinf: Haemophilus influenzae; SPI: sinopulmonary infection; S VZV: Severe VZV infection i.e. pneumonitis; IPI: Invasive Pneumococcal Infection; HLH: Hemophagocytic Lymphohistiocytosis; Y: Yes; N: No.

*siblings from Family 1

**siblings from family 2

^patients who had abnormal lymphocyte subsets

Table 2: Details of hematopoietic stem cell transplantation

Patient	Age@ HSCT (Year)	Donor	Source	Conditioning	GvHD Prophylaxis	Neutrophil/CD3 engraftment***	Viral reactivation Timing	Chimerism % donor	GvHD Site/grade	Off IVIG	Outcome Time of F/U	Reason for death
Pt 1	17	MUD 10/10	PBSC	Mel 140/Flu 150/Alem 1	CSA/MMF	D+13/+45	CMV/HHV6 D+37/+34	CD15 93% CD19 97% CD3 100%	Skin, GI	Y	A&W 12y	
Pt 2	8	MUD 10/10	BM	Treo 42/Cyclo 200/Alem 1	CSA/MMF	D+14/+60	ADV D0	CD15 25% CD19 48% CD3 76%	Skin GII	Y	A&W 8y	
Pt 3	1	MUD 10/10	CB	Treo 42/Flu 150	CSA/MMF	D+23/+17	EBV/ADV D0	WB 100%	Skin GIII Gut GI	Y	hemiplegia, developmental delay, 4y	
Pt 4	8	MUD 10/10	PBSC	Treo 42/Flu 150/Alem 1	CSA/MMF	D+14/+46	EBV D+39	WB 100%	Skin GII	Y	died	EBV encephalitis, D+76
*Pt 5	9	MUD 10/10	PBSC	Mel 140/Flu 150/Alem 1	CSA	D+13/+180	EBV D+87	WB 100%	No	Y	A&W 22y	
*Pt 6	5	MUD 10/10	PBSC	Treo 42/Flu 150/Alem 1	CSA/MMF	D+11/+59	N/A	WB 100%	No	Y	A&W 17y	
**Pt 7	8	MUD 9/10	PSBC	Mel 140/Flu 150/Alem 1	CSA/MMF	D+11/NA^	CMV/ADV D+31/+71	WB 100%	Gut GIII	N/A	died	chronic, intractable CMV & adenovirus enteritis with secondary gut cGvHD, D+290
**Pt 8	12	MUD 9/10 DQ	BM	Bu 9.5 (target AUC 60, RIC)/ Flu 180/Alem	CSA/MMF	D+15/+88	EBV D+248^^	WB 100%	Skin GIII	Y	died	intractable skin cGvHD, CNS PML,

Pt 9	5	MUD 10/10	PBSC	Mel 140/Flu 150/Alem 1	CSA/MMF	D+17/+9m	BK virus D+7	CD15 85% CD3 100%	Skin GII	Y	A&W 1y
Pt 10	13	MSD 10/10	BM	Bu (target to AUC 60, RIC)/ Flu 180/ATG 40		D+40/+102	N/A	WB 100%	No	No	A&W 9m
Pt 11	3	Haplo TCR a/b depleted	PBSC	Treo 42/TT 10/Flu 160/ ATG15	CSA/MMF	D+35/+34^^	EBV D+68^^	WB 100%	No	No	A&W 8m

Pt: Patient; MUD: Matched unrelated donor; MSD: Matched sibling donor; PBSC: Peripheral blood stem cells; BM: Bone marrow; CB: Cord blood; F/U: Follow up; Neut: Neutrophil; GvHD: Graft versus Host Disease; IVIG: Immunoglobulin; LPD: Lymphoproliferative Disease; PML: Progressive Multifocal Leucoencephalopathy; A/W: Alive and Well; D: Day; N/A: Not Applicable; WB: Whole blood; Y: Yes; y: year, m: month; Treo: treosulfan, dose g/m²; TT: thiotepa, dose mg/kg; Bu: busulphan; Mel: melphalan, dose mg/m²; Flu: fludarabine, dose mg/m²; Cyclo: cyclophosphamide, dose mg/kg; Alem: alemtuzumab, dose mg/kg; ATG: anti-thymocyte globulin, dose mg/kg; EBV: Epstein Bar virus; ADV: Adenovirus; HHV6: Human Herpes Virus 6; CMV: cytomegalovirus.

*siblings from Family 1

**siblings from family 2

***CD3 engraftment: CD3 $\geq 0.3 \times 10^9/L$

^ The patient always had CD3 $> 0.3 \times 10^9/L$ due to receiving EBV CTLs

^^The patient was on immunosuppressive treatment