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Capsule Summary

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

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

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***To the Editor*,**

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

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

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

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

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

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

CTPS1 deficiency is a serious life-limiting immunodeficiency with a high risk of death from VZV and EBV in the first decade of life. Seven (41%) of 17 patients worldwide with CTPS1 deficiency have died, three post and four prior to HSCT (one from fulminant VZV and the other three from fulminant EBV LPD). These deaths were prior to clinical availability of rituximab. However, mild clinical phenotype has previously been described [5]. HSCT can be curative but is not without potential risks and complications. Kucuk et al also reported two siblings with this mutation who had successful transplantation [6]. The current report is the largest series of children with CTPS1 deficiency who have undergone HSCT.The overall survival post-HSCT in this series was 72% which is slightly lower than seen after HSCT for other combined PIDs[7]. Pre-transplantation, extra-nodal EBV-driven LPD of the brain and lung as well as fulminant VZV pneumonitis requiring ventilation in intensive care are major risks. The post-transplantation course can be challenging to even the specialist centres because of re-activation of EBV and other herpes viruses, particularly in the brain and gastrointestinal tract, but also because of the risk of unusually severe skin and gut cGvHD, the latter which may be partly

fuelled by ongoing underlying low grade chronic viral infection. Both patients that developed fatal GvHD had transplants from 9/10 matched unrelated donors. Viral reactivation can be observed prior to donor T-lymphocyte engraftment post-transplant and perhaps 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 recommend early transplantation before the onset of end-organ damage and for patients without fully matching family or unrelated donors, the consideration of ex-vivo T-cell depletion strategies.

The authors confirm there is no conflict of interest.

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References

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

5. Trück J, Kelly DF, Taylor JM, Kienzler A, Lester T, Seller A et al. Variable phenotype and discrete alterations of immune phenotypes in CTP synthase 1 deficiency: Report of 2 siblings. J Allergy Clin Immunol, 2016; Volume 138, Issue 6, Pages 1722–1725.

6. Kucuk ZY, Zhang K, Filipovich L, Blessing J. CTP Synthase 1 Deficiency in Successfully Transplanted Siblings with Combined Immune Deficiency and Chronic Active EBV Infection. J Clin Immunol. 2016 Nov; 36(8):750-753.

7. Dvorak CC, Cowan MJ. Hematopoietic stem cell transplantation for primary immunodeficiency disease. Bone Marrow Transplant. 2008 Jan; 41(2):119-26.

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
		SPI	EBV-LPD	S VZV	Chronic Diarrhoea	HLH	Viral viremia	IPI	lymphoma				
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,

				1							D+464
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 ≥ 0.3 x 10^9/L

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

^^The patient was on immunosuppressive treatment