Medical and Clinical Research: Open Access

Research Article

Human Cytomegalovirus Infection Associated with Low Insulin Secretion in a Type 1 Diabetic Population in Pointe Noire

Aladin ATANDI BATCHY[1,2], Luc Magloire Anicet BOUMBA[1,3,5*], Charley ELENGA-BONGO[1,2], Ghislain LOUBANO VOUMBI[1,4], Freddy Saturnin POUKI[1], Fredy KIBOUILOU[1,2], Ange MALONGA[1], Donatien MOUKASSA[1] and Martin DIATEWA[1]

[1]*Faculty of Health Sciences, Marien Ngouabi University, BP: 69 Brazzaville, Congo.*
[2]*Department of Endocrinology and Metabolic Diseases, General Hospital Adolph Sicé, Pointe-Noire Congo.*
[3]*Medical and morphological analysis laboratory General Hospital Loandjili, Pointe-Noire Congo.*
[4]*Medical analysis laboratory, Dolisie General Hospital, Dolisie, Congo.*
[5]*Pointe-Noire Research Zone, National Institute for Research in Health Sciences (IRSSA) Brazzaville, Congo.*

Corresponding Author Information

Dr. Luc Magloire Anicet BOUMBA

Biologist PhD in Molecular and Tropical Virology and Oncology, Marien NGOUABI Univserity, Congo, Tel : (+242) 056601040.

Received: February 10, 2022; **Accepted:** March 17, 2022; **Published:** March 22, 2022

Citation: BATCHY AA, BOUMBA LMA, ELENGA-BONGO C, et al. Human Cytomegalovirus Infection Associated with Low Insulin Secretion in a Type 1 Diabetic Population in Pointe Noire . Med Clin Res Open Access. 2022; 3(1):1-5.

ABSTRACT

Viral infections are one of the triggers and aggravators factors type 1 diabetes (T1D) development. Among these infections, human cytomegalovirus infection affects 60-90% of the world's population.

The aim of this study was to describe the metabolic consequences of Cytomegalovirus infection in T1D subjects. We conducted a descriptive cross-sectional study over 6 months between June and November 2021. A total of 72 T1D subjects were enrolled. The following laboratory tests were performed: fasting blood glucose, HbA1c, C peptide, lipid profile and CMV serology. The mean age of the patients was 19. 8±4.3 years with a sex ratio (M/F) of 1.4. CMV serology was positive in 75% of T1D patients. We noticed a disturbance of the biochemical markers in T1D+CMV+ patients. The homeostasis model of β-cell function (HOMA β) evaluation was significantly lower in T1D+CMV+ patients compared to T1D+CMV- patients. Blood glucose (8.69±5.30 vs 7.08±6.71 P=0.009), HbA1C (10.42±2.85 vs 8.77±2.90 P=0.009), TC (2.04±0.37 vs 1.97±0.28 P=0.0039), HDL-C (0.26±0.11 vs 0.19±0.007 P=0.0091), LDL-C (1.25±0.55 vs 1.20±0.50 P= 0.0039), were higher in T1D+CMV+ vs T1D+CMV-. However, creatinine (8.20±1.80 vs 9.13±1.07 P=0.0039), C peptide (0.15±0.003 vs 0.13±0.002 P=0.009) were higher in T1D+CMV- than in T1D+CMV+. The present study showed that CMV infection was associated with disturbed metabolic characteristics in T1D and deep insulin deficiency.

Keywords

Type 1 diabetes, CMV infection, Biochemical markers, Pointe-Noire.

Introduction

The term diabetes describes a complex metabolic disorder characterized by chronic hyperglycaemia resulting from defects in insulin secretion, insulin action, or both [1].

The prevalence of diabetes worldwide in 2013 was 382 million people. The International Diabetes Federation (IDF) estimates that by 2035, this number will reach 592 million people [1]. It affects 5.1% of people in Africa [1]. According to IDF estimations, approximately 96,000 children under the age of 15 develop type 1 diabetes annually worldwide [2].

The majority of diabetes results from an interaction between gene and environment. It is recognized that viral infections play a major role as environmental factors in onset, maintening, or exacerbation of metabolic disorders observed in diabetes [3].

In addition to the classic forms of diabetes type 1 (T1D) and type 2 (T2D), certain viruses have been identified as probable etiologies for diabetes development, namely enteroviruses in T1D [4], hepatitis C virus [5] and human immunodeficiency virus (HIV) in T2D [6].

Epidemiological, clinical and pathological studies in humans have suggested that viral infections may be one of the precipitating and aggravating factors for the development of T1D [7,8]. Human cytomegalovirus (CMV), a member of the herpesviridae family, is an ubiquitous pathogen that consistently infects 60-90% of the world's population [9]. During active CMV infection, patients often suffer from immunological dysfunction and autoimmune phenomena such as autoantibodies [10]. Multiple case reports describe primary, reactivating or persistent CMV infections as potential triggers for autoimmune endocrine diseases such as T1D [9].

In current state of studies, it is difficult to confirm or deny whether other viruses identified in the Caucasian population (rubella, Epstein-Barr virus) are also associated with T1D in Africans. To our knowledge, no study in Congo has been conducted in that way. Thus, the objective of our work was to describe the metabolic consequences of Cytomegalovirus infection in T1D subjects in Pointe Noire.

Materials And Methods

Study population

We conducted a cross-sectional descriptive study with prospective data collection. The study lasted 6 months, between June and November 2021.

Our population of study consisted of type 1 diabetic children from *"LIFE OF CHILDREN"* program at the Adolphe Sice General Public Hospital in Pointe-Noire. We included all T1D patients aged of 25 years or more at discovery of the illness. Patients living with T1D since 15 years were included in our study.

Fasting blood sample

The socio-demographic data of patients were collected on a pre-established survey form. Then we collected 5 ml of blood in 2 tubes, dry and EDTA respectively from the elbow using vacuum needle after disinfection with 70% alcohol. The blood on dry tube was centrifuged for 10 minutes at 3000 rpm and the serum obtained was aliquoted into cryotubes and stored at -25°C until use. Blood in EDTA tube was used for the determination of HbA1c.

Biochemical analysis

All biochemical analysis were performed twice using the same batch of reagents kits each time. Plasma glucose and HbA1c levels were determined with Cobas C 311 (Roche Diagnostics, HITACHI, Germany).

Total cholesterol, high density lipoprotein cholesterol (HDL-C) and triglycerides were determined using standard enzymatic techniques. Low density lipoprotein cholesterol (LDL-C) was calculated using the Fridewalds formula [11]. C peptide was measured using the ELISA kit "ELISA C PEPTIDE DONOV, France".

Determination of Insulin Secretion

Assessment of insulin sensitivity homeostasis model (HOMA-β) was calculated in fasting samples to assess langherans β-cells function, using the following equation:

$$HOMA-\beta(CP) = \frac{0.27 \times \text{fasting C peptide (/mL)}}{\text{Fasting blood sugar} - 3.5\ mmol/L}$$

This equation has been validated by insulin clamp techniques.

Virological Analyses

Serum samples were screened for CMV detection using the commercial fourth generation enzyme-based CMV (IgM and IgG) ELISA technique according to recommendations of the manufacturer's (IBL^{R} INTERNATIONAL GMBH Hamburg, Germany). The results of the assay were expressed quantitatively as the ratio (R) of the optical density of the test sample to the calculated cut-off absorbance, as recommended by the manufacturer. Sera with ratios > 1.1 were considered positive, sera with R values of 0.9 to 1.1 were recorded as indeterminate and retested, while those with R values < 0.9 were considered negative.

Ethical approval

This study was conducted in accordance with the guidelines of the Declaration of Helsinki and was approved by the Health Sciences Study Committee of The Republic of Congo. All patients gave informed consent or parents' consent for minors.

Statistical analysis

Data were analysed using SPSS 12.0 (SPSS Inc., Chicago, IL, USA). Results are presented as percentages and mean ± standard deviation. An exact Fischer test was used to compare categorical variables. Unpaired t-tests and analysis of variance (ANOVA) were used to compare normally distributed data between study groups. The 95% confidence interval (CI) was calculated. P values less than 0.05 were considered significant.

Results

Characteristics of the Study Population and CMV Serological Profile

Our population of study consisted of more than 58% men (Table 1). The mean biological age of all patients was 19.8±4.3 years with extremes ranging from 5 to 35 years. At the time of discovery of the disease, 69.4% of the patients were between 15-25 years of age. The average age of living with T1D was 3.9±2.02 years. CMV serology was positive in 75% of the patients in the study population.

Table 1: Socio-demographic characteristics of the study population and CMV serological profile.

Characteristics	Effective (n)	Pourcentage (%)
Gender		
Male	42	58.33
Female	30	41.66
Biological age (in year)		
Mean age (in year)	19.8±4.3	
]5-15[	6	8.3
]15-25[	58	80.5
]25-35[	8	11.1
Age at the discovery of TD1 (in year)		
Mean age (in year)	16.3±3.41	
]5-15[	22	30.5
]15-25[	50	69.4
Number of year living with TD1 (year)		
Mean age (in year)	3.9±2.02	
]2-4[	34	47.2
]4-6[	16	22.2
]6-10[	22	30.5
CMV serology profil		
Positive	54	75
Negative	18	25

Diabetic phenotype according to CMV serology

Clinical and metabolic characteristics of CMV-positive and CMV-negative T1D patients are shown in Table 2.

Clinical features

No difference statistically significant was observed between CMV+ and CMV- T1D with respect to the biological age of the patients and the age of living with T1D (p>0.05). On the other hand, a statistically significant difference was observed between the two groups with respect to the age of discovery of T1D (p=0.043). Furthermore, there was a similarity between the two groups with regard to height and BMI. However, a significant difference was noted between the two groups in terms of patient weight (p=0.041).

Metabolic characteristics

A significant decrease of HOMA index, TG and creatinemia was observed in the group of CMV+ T1D patients. On the other hand, a significant trend towards an increase was noted for the other metabolic parameters in the same group.

Table 2: Clinical and metabolic characteristics of T1D patients according to CMV serology profile.

Diabetic Phenotype	CMV IgG (+) DT1	CMV IgG (-) DT1	P value
Clinicalfeatures			
Biological age (year)	20. 07 ±4.42	21. 88 ±4.07	0.82
Age of living with T1D (years)	3. 66 ±2.14	5. 33 ±3.12	0.81
Age of discovery of T1D (year)	16. 22 ±4.29	16. 55 ±4.66	0.043
Size (m)	1. 55 ±0.15	1. 61 ±0.03	0.71
Weight (Kg)	64. 67 ±11.92	61. 58 ±7.76	0.041
BMI kg/m2	22. 61 ±3.89	23. 72 ±3.11	0.882
Metabolic characteristics			
Blood glucose (mmol/L)	8. 69 ±5.30	7. 08 ±6.71	0.009
HbA1C (%)	10. 42 ±2.85	8. 77 ±2.90	0.009
TC (g/L)	2. 04 ±0.37	1. 97 ±0.28	0.0039
LDL-C (g/L)	1. 25 ±0.55	1. 20 ±0.50	0.0039
HDL-C (g/L)	0. 26 ±0.11	0. 19 ±0.007	0.0091
TG (g/L)	0. 81 ±0.22	1. 04 ±0.34	0.0039
Creat (mg/dl)	8. 20 ±1.80	9. 13 ±1.07	0.0039
C-Peptide (ng/ml)	0. 15±0.03	0. 13 ±0.02	0.009
HOMA β*10E-5	1. 79±1.51	3. 64 ±2.46	0.0001

Data are presented as mean ± standard deviation.

T1D+CMV+= CMV-positive T1D patient; T1D +CMV-= CMV-negative T1D patient; BMI= body mass index; HbA1C= glycated haemoglobin; TC= total cholesterol; LDL-C= low-density lipoproteins; HDL-C= high-density lipoproteins; TG= triglycerides; C-peptide = Connecting Peptide; HOMA β= β-cell homeostasis assessment model.

Discussion

The association between type 1 diabetes and cytomegalovirus infection is no longer in doubt [12]. The aim of the present study was to describe the metabolic consequences of cytomegalovirus infection in type 1 diabetic subjects in Pointe Noire.

The average biological age of the patients was 19.8±4.30 years. This age is relatively high compared to that found by *PAMBOU et al. (2019)* in GABON. This difference can be explained by the fact that we included subjects over 20 years old in our study, unlike the Gabonese study which was limited to patients aged 15 years or less.

At the time of diabetes discovery, the average age of patients was 16.3 years. This average is also observed in several studies in Africa [13,14]. In contrast, Caucasian subjects appear to be younger at diagnosis than those in our study. According to these observations, T1D is rarely diagnosed in children under 5 years of age *in* Africa as suggested by *UGEGE et al. (2012).*

Serological profiling has shown that more than 2/3 of the type 1 diabetic population are carriers of CMV infection. Several studies in the literature have also observed this [9,15,16]. This can be explained by the fact that CMV plays an important role in diabetogenesis. Indeed, it has been postulated that there is T-cell cross-reactivity between CMV and GAD 65 in pancreatic islet β cells [17]. The age of living with T1D is variable depending on CMV serological status. In this study, a relatively young age of 3.66 years was observed in T1D+CMV+ patients and the disturbance of biological markers, whereas this age was 5.33 years in T1D+CMV- patients. This decreasing trend in the T1D+CMV+ group was also observed in the BMI of the patients. These observations indicate that CMV infection may accelerate the onset of diabetes symptoms, leading to early discovery and complications. In parallel, King et al. (1983) and Banatvala *et* al. (1985), also found the same observations in their respective studies on T1D and HHV8 and T1D and Rubella [9,18]. In this study all metabolic parameters

were disturbed with significant differences. An increasing trend was observed between the T1D +CMV+ versus T1D +CMV- groups for the following parameters: HbA1C, TC, blood glucose, HDL and LDL. Our results are in line with studies performed by Jerrald *et al. (2015)* and *Yu et al. (2011)* [19,20]. The increase in HbA1c in T1D+CMV (+) could be explained by the fact that CMV induces a disturbance in glucose regulation by increasing GLUT4 activity which increases glucose uptake leading to hyperglycaemia [18]. Several authors such as Chukkapalli et *al.* (2012); *Gudleski-O'Regan* et *al.* (2012) *and Williamson CD et al. (2011)* have obtained the same results as ours [21-23]. As for the disruption of lipid markers in T1DM+CMV (+), several hypothesis have been put forward regarding CMV infection in T1D. *Chukkapli et al. (2012)* revealed that lipid disruption during CMV infection is due to the interaction of virions and cellular lipids [21]. In contrast, *Gudleski-O'Regan et al* (2012) suggested that this variation is due to a plasma membrane receptor that regulates lipid metabolism and that is elevated early after CMV infection, resulting in a decrease in intracellular cholesterol concentration [22]. *Williamson et al. (2011)* showed that this disruption is due to the UL37 protein exon [21]. Furthermore, HOMA, C peptide, creatinine and TG were significantly lower in the T1D+CMV+ group than in the T1D+CMV- group. Few studies have examined the detrimental role of CMV on renal function and in particular in the context of T1D, however we can incriminate the role of the imbalance of the inflammatory system. Indeed, CMV is an established risk factor for renal alloimplant rejection [23,24]. CMV infection has been implicated in chronic alloimplant dysfunction and implant loss [25]. The reduction in the incidence of acute rejection in patients receiving CMV prophylaxis was mainly explained by the prevention of the development of CMV disease and viremia [26].

However, the beneficial effect on the incidence of acute rejection in renal transplant recipients has been linked to valacyclovir prophylaxis [27]. However, our study cannot establish a direct link, especially in the context of T1D.

Finally, we assessed insulin secretion in both groups using HOMA β (CP). It was observed that low insulin secretion in the T1D+CMV+ group. These data have also been observed in several studies in the literature (252-267). This could be explained by the fact that pancreatic damage is greater in T1D+CMV (+) subjects compared to T1D+CMV (-) subjects, as CMV has a lytic action on the β-cells of the islets of Langerhans responsible for insulin production [28] tabtabl.

Conclusion

In this study, the authors observed a fairly late age of diabetes discovery. They also noted a disturbance of metabolic markers in T1D subjects when they are also carriers of a CMV infection. This T1D+/CMV+ association showed, thanks to the HOMA index, the existence of a deep insulin deficiency. The continuation of this work throughout the country would allow a definition of the national parameters linked to this association.

References

1. WHO (2016) Global Diabetes Report.
2. IDF. (2017) Diabetes. 8th Edition.
3. Mathie Tenenbaum AB, Philippe Froguel. Physiopathology of diabetes (2018) Revue Francophone Of Laboratory. 2018 ;502:26-32.
4. Didier Hober, Laurent Andréoletti, Christine Hober, Sandrine Belaïch, Marie Christine,Vantyghem, Jean Lefèbvre, Pierre Wattré. Enterovirus and type 1 diabetes. Medecine science. 1998;14:398-403.
5. N. Kabbaj, I. Errabih, M. Guérida, H.El Atmani, K. Benabed, Z. Al Hamany, M. Mohammadi, A. Benaissa. Viral hepatitis c and diabetes: influence of diabetes on the evolution of hepatopathy. Ann. Endocrinol. 2006;67(3):233-237.
6. L. Nguewa, P. Riveline N. Baldé E. Sobngwi, C.M., E. Lontchi-Yimagou, SP. Choukem F. Gautier. *Viral infections and diabetes in Africa.* Medicine of Metabolic Diseases. 2015;9:151-157.
7. Hyöty H, Taylor Kw. The role of viruses in human diabetes. Diabetologia. 2002;45:1353-61.
8. Jun HS, Yoon JW. A new-look at viruses in type 1 diabetes. Diabetes Metab Res Rev. 2003;19:8-31.
9. Halenius A, Hengel H. Human Cytomegalovirus and Autoimmune Disease. BioMed Research International. 2014;1-15.
10. Marc S Horwitz, Sarvetnick N. Viruses and autoimmunity. Annals Of The Institut Pasteur. 1996;7(2):81-6.
11. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1992;18:499-502.
12. Chen S, Jm De Craen A, Raz Y, Derhovanessian E, Vossen Ctm A, Westendorp Gj R, et al. Cytomegalovirus seropositivity is associated with glucose regulation in the oldest old. Results from the leiden 85-plus study. Immun Ageing. 2012;9:18.
13. Pambou Damiens. International Journal of Pediatrics and Adolescent Medicine. 2019;6:87.
14. Ugege O, Ibitoye PK, Jiya NM. Childhood diabetes mellitus in sokoto, north-western Nigeria: A ten year review. Sahel Med J. 2013;16:97-101.
15. Basma Abdel-Moez Ali andWafaa K. M. Mahdi association of cytomegalo virus with type 1 diabetes mellitus among children in minia governorate. Afr J Cln Exper Microbiol. 2015;16(3):86-91.
16. King M.L, Shaikh A. Bidwell D. Voller A. Banatvala J.E. Coxsackie-B-virus specific IgM responses in children with insulin-dependent diabetes mellitus. Lancet. 1983; i: 1397-1399.
17. Hoebert S. Hiemstra, Nanette C. Schloot, Peter A. van Veelen, Sabine J. M. Willemen, Kees L. M. C. Franken, Jon J. van Rood, Rene' R. P. de Vries, Abhijit Chaudhuri, Peter O. Behan, Jan W. Drijfhout, and Bart O. Roep**:** Cytomegalovirus in autoimmunity: T cell crossreactivity to viral antigen and autoantigen glutamic acid decarboxylase PNAS. 98(7).

18. Banatvala J.E., Schernthaner G. ,Schober E. Coxsackie B, mumps, rubella and cytomegalovirus specific IgM responses in patients with juvenile-onset insulin-dependent diabetes mellitus in Britain, Austria and Australia. Lancet. 1985; i :1409-1412.
19. Rector JL, Thomas GN, Burns VE, Dowd JB, Herr RM, Moss PA, et al. Elevated HbA1c levels and the accumulation of differentiated T cells in CMV+ individuals. Diabetologia. 2015.
20. Yu Y, Maguire TG, JC A. Human cytomegalovirus activates glucose transporter 4 expression to increase glucose uptake during infection. J Virol. 2011;85:1573-80.
21. Chukkapalli V, Heaton NS, RG. Lipids at the interface of virus-host interactions. Curr Opin Microbiol. 2012;15:512-8.
22. Gudleski-O'Regan N, Greco TM, Cristea IM, T. S, I.M.C. Increased expression of LDL receptor-related protein 1 during human cytomegalovirus infection reduces virion cholesterol and infectivity. Cell Host Microbe. 2012;12:86-96.
23. Reischig T, Jindra P, Svecová M, Kormunda S, Opatrný K Jr, V.T. The impact of cytomegalovirus disease and asymptomatic infection on acute renal allograft rejection. J Clin Virol. 2006;36(2):146-51.
24. T R. Cytomegalovirus-associated renal allograft rejection: new challenges for antiviral preventive strategies. Expert Rev Anti Infect. 2010;8(8):903-10.
25. Dzabic M, Rahbar A, Yaiw KC, Naghibi M, Religa P, Fellström B, et al. Intragraft cytomegalovirus protein expression is associated with reduced renal allograft survival. Clin Infect Dis. 2011;53(10):969-76.
26. Kalil AC, Levitsky J, Lyden E, Stoner J, AG.F. Meta-analysis: the efficacy of strategies to prevent organ disease by cytomegalovirus in solid organ transplant recipients. Ann Intern Med. 2005;143(12):870-80.
27. Reischig T, Jindra P, Mares J, Cechura M, Svecová M, Hes O, et al. Valacyclovir for cytomegalovirus prophylaxis reduces the risk of acute renal allograft rejection. Transplantation. 2005;79(3):317-24.
28. Ekman I, Vuorinen T, Knip M. Early childhood CMV infection may decelerate tne progression to clinical type 1 diabetes. Pediatr Diabetes. 2019;20:73-77.