Table 2. Genotype/allele frequencies for *ABCB1*, *NR1I2*, *UGT1A1*, *SLCO1B1* and *CYP3A5* in patients with and without nephrolithiasis

		Genotype frequency				Allele frequency		
	Amino acid	nephrolithiasis ($n=31$)	no nephrolithiasis ($n=47$)	*P* value[a]		nephrolithiasis ($n=31$)	no nephrolithiasis ($n=47$)	*P* value[a]
ABCB1 (P-glycoprotein)					*ABCB1* (P-glycoprotein)			
193 A→G, rs3842					193 A→G, rs3842			
A/A		16 (52)	27 (57)		A	46 (74)	68 (72)	0.81
A/G		14 (45)	14 (30)	0.24	G	16 (26)	26 (28)	
G/G		1 (3)	6 (13)					
365 T→C, rs3213619					365 T→C, rs3213619			
T/T		28 (90)	37 (79)		T	59 (95)	84 (89)	0.33
T/C		3 (10)	10 (21)	0.23	C	3 (5)	10 (11)	
C/C		0	0					
1236 T→C, rs1128503	Gly412Gly				1236 T→C, rs1128503			
T/T		7 (23)	15 (32)		T	33 (53)	52 (55)	0.80
T/C		19 (61)	22 (47)	0.48	C	29 (47)	42 (45)	
C/C		5 (16)	10 (21)					
2677 T→A/G, rs2032582	A:Ser893Thr				2677T→A/G, rs2032582			
T/T	G:Ser893Ala	5 (16)	5 (11)		T	26 (42)	30 (32)	
T/A		6 (19)	5 (11)		A	14 (23)	17 (18)	0.20
G/G		3 (10)	10 (21)	0.45	G	22 (35)	47 (50)	
G/T		10 (32)	15 (32)					
G/A		6 (19)	12 (26)					
A/A		1 (3)	0					
3435 C→T, rs1045642	Ile1145Ile				3435 C→T, rs1045642			
C/C		10 (32)	22 (47)		C	36 (58)	65 (69)	0.16
C/T		16 (52)	21 (45)	0.35	T	26 (42)	29 (31)	
T/T		5 (16)	4 (9)					
NR1I2 (PXR)					*NR1I2* (PXR)			
131 A→C, rs1523127					131 A→C, rs1523127			
C/C		1 (3)	6 (13)		C	20 (32)	35 (37)	0.53
C/A		18 (58)	23 (49)	0.38	A	42 (68)	59 (63)	
A/A		12 (39)	18 (38)					
370 G→A, rs3732359					370 G→A, rs3732359			
G/G		8 (26)	16 (34)		G	35 (56)	53 (56)	1.00
G/A		19 (61)	21 (45)	0.37	A	27 (44)	41 (44)	
A/A		4 (13)	10 (21)					
522 C→T, rs3732360					522 C→T, rs3732360			
C/C		8 (26)	15 (32)		C	35 (56)	53 (56)	1.00
C/T		19 (61)	23 (49)	0.60	T	27 (44)	41 (44)	
T/T		4 (13)	9 (19)					
1195 A→C, rs3814057					1195 A→C, rs3814057			
A/A		4 (13)	11 (23)		A	27 (44)	44 (47)	0.69
A/C		19 (61)	22 (47)	0.39	C	35 (56)	50 (53)	
C/C		8 (26)	14 (30)					

1232 T→C, rs3814058					1232 T→C, rs3814058			
T/T		4 (13)	10 (21)		T	27 (44)	41 (44)	1.00
T/C		19 (61)	21 (45)	0.37	C	35 (56)	53 (56)	
C/C		8 (26)	16 (34)					
44477 T→C, rs1523130					44477 T→C, rs1523130			
T/T		1 (3)	6 (13)		T	19 (31)	34 (36)	0.48
T/C		17 (55)	22 (47)	0.38	C	43 (69)	60 (64)	
C/C		13 (42)	19 (40)					
63396 T→C, rs2472677					63396 T→C, rs2472677			
T/T		18 (58)	24 (51)		T	45 (73)	68 (72)	0.98
T/C		9 (29)	20 (43)	0.38	C	17 (27)	26 (28)	
C/C		4 (13)	3 (6)					
UGT1A1					*UGT1A1*			
*28[b]					*28[b]			
*1/*1		27 (87)	44 (94)		*1	57 (92)	91 (97)	0.21
*1/*28		3 (10)	3 (6)	0.50	*28	5 (8)	3 (3)	
*28/*28		1 (3)	0					
211 G→A, rs4148323	Gly71Arg				211 G→A, rs4148323			
G/G		19 (61)	30 (64)		G	49 (79)	73 (78)	0.85
G/A		11 (36)	13 (28)	0.61	A	13 (21)	21 (22)	
A/A		1 (3)	4 (9)					
c.211 T→C, rs10929303					c.211 T→C, rs10929303			
T/T		0	0		T	11 (18)	6 (6)	0.033
T/C		11 (35)	6 (13)	0.025	C	51 (82)	88 (94)	
C/C		20 (65)	41 (87)					
339 G→C, rs1042640					339 G→C, rs1042640			
G/G		0	0		G	11 (18)	4 (4)	0.012
G/C		11 (35)	4 (9)	0.007	C	51 (82)	90 (96)	
C/C		20 (65)	43 (91)					
440 G→C, rs8330					440 G→C, rs8330			
G/G		1 (3)	0		G	12 (19)	4 (4)	0.006
G/C		10 (32)	4 (9)	0.007	C	50 (81)	90 (96)	
C/C		20 (65)	43 (91)					
SLCO1B1					*SLCO1B1*			
388 A→G, rs2306283	Asn130Asp				388 A→G, rs2306283			
A/A		14 (45)	24 (51)		A	42 (68)	68 (72)	0.54
A/G		14 (45)	20 (43)	0.83	G	20 (32)	26 (28)	
G/G		3 (10)	3 (6)					
521 T→C, rs4149056	Val174Ala				521 T→C, rs4149056			
T/T		20 (65)	31 (66)		T	51 (82)	75 (80)	0.71
T/C		11 (36)	13 (28)	0.34	C	11 (18)	19 (20)	
C/C		0	3 (6)					
CYP3A5					*CYP3A5*			
14 T→C, rs15524					14 T→C, rs15524			
T/T		16 (52)	25 (53)		T	46 (74)	67 (71)	0.70
T/C		14 (45)	17 (36)	0.50	C	16 (26)	27 (29)	
C/C		1 (3)	5 (11)					

[a]By Fisher's exact test.
[b]*1, reference sequence $A(TA)_6TAA$; *28, $A(TA)_7TAA$.

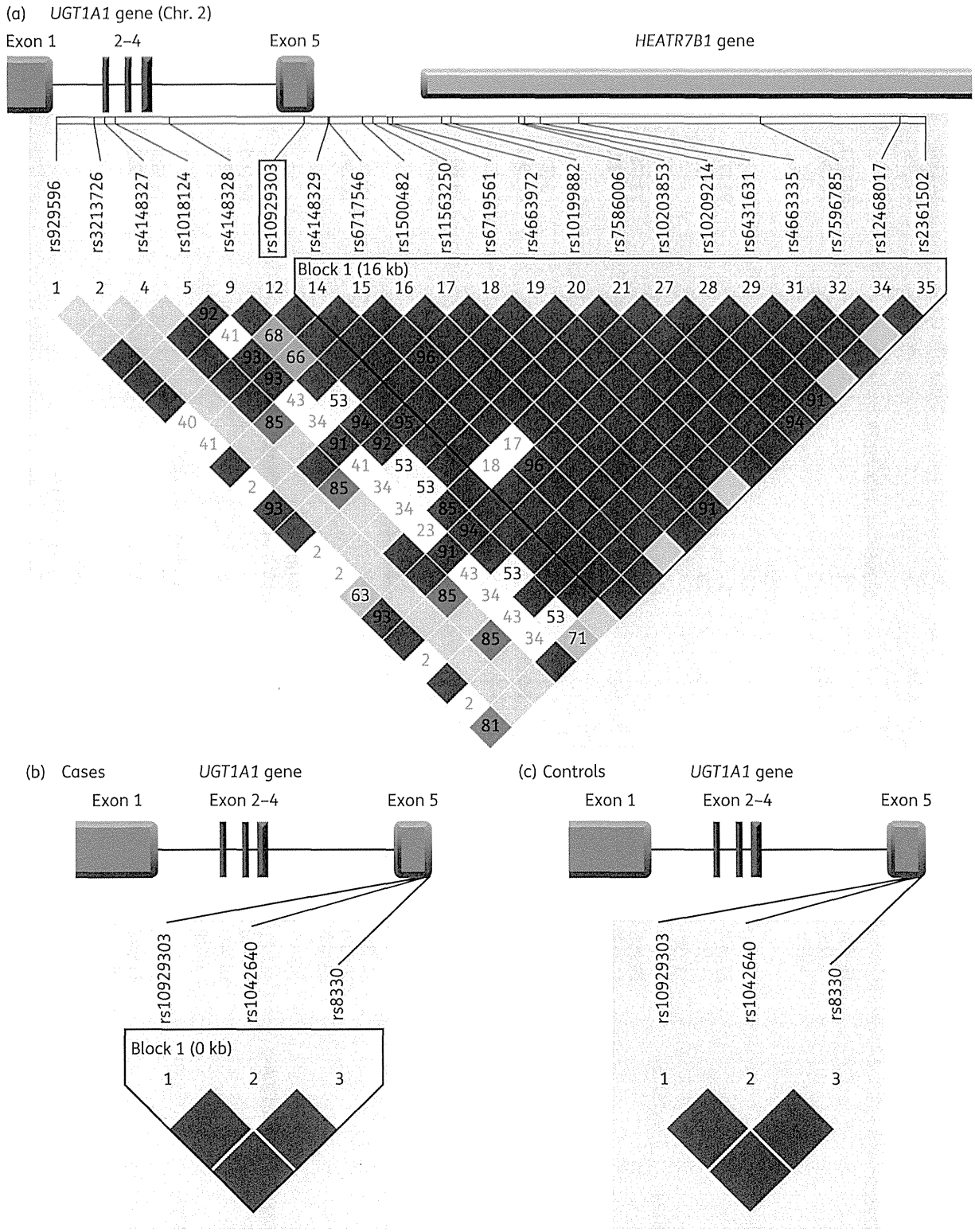

Figure 1. Pairwise linkage disequilibrium analysis of *UGT1A1* and surrounding SNPs. (a) Pairwise linkage disequilibrium analysis of *UGT1A1* and surrounding SNPs using HapMap Japanese samples. SNP c.211 (rs10929303) of the UGT1A-3′-UTR is in tight linkage disequilibrium with the gene next to *UGT1A1* (*HEATR7B1*). Two SNPs at 339 (rs1042640) and 440 (rs8330) of the UGT1A-3′-UTR are not shown in (a), but they are located close to c.211, as shown in (b) and (c). Pairwise linkage disequilibrium analysis of the three risk SNPs in the UGT1A-3′-UTR in (b) 31 cases (patients with atazanavir-induced nephrolithiasis) and (c) 47 controls. The difference between (b) and (c) suggests that the number of risk haplotypes is greater in case patients than in control patients. Estimates of *D′* for SNPs are shown as numbers in the Argyle box. Dark red shading indicates strong linkage disequilibrium (*D′* >0.9). Light blue shading indicates high *D′* values (>0.99) with low statistical significance [LOD (log of the odds) <2].

shows the results of pairwise linkage disequilibrium analysis of *UGT1A1* and SNPs around them derived from HapMap data for the Japanese. On the other hand, there was no difference in the distribution of 16 other SNPs in *ABCB1*, *NR1I2*, *SLCO1B1* and *CYP3A5* between cases and controls. The distribution of UGT1A1*28 was also not different.

Association of genotypes with atazanavir-induced nephrolithiasis

Univariate analysis showed a significant association between atazanavir-induced nephrolithiasis and genotype T/C versus C/C at c.211 (OR=3.8; 95% CI, 1.22–11.6; P=0.022), genotype G/C versus C/C at position 339 (OR=5.9; 95% CI, 1.68–20.9; P=0.006) and genotype G/G or G/C versus C/C at 440 (OR=5.9; 95% CI, 1.68–20.9; P=0.006) of the UGT1A-3′-UTR (Table 3). No other SNPs, including UGT1A1*28, showed any association with nephrolithiasis. Furthermore, basic demographics and established risk factors for nephrolithiasis were not associated with nephrolithiasis, except for infection with hepatitis C virus, which was marginally associated with nephrolithiasis (OR=8.8; 95% CI, 0.98–79.9; P=0.052).

Multivariate analysis adjusted for sex, age and hepatitis C infection identified genotype T/C versus C/C at position c.211 (adjusted OR=3.7; 95% CI, 1.13–11.9; P=0.030), genotype G/C versus C/C at 339 (adjusted OR=5.8; 95% CI, 1.56–21.3; P=0.009) and genotype G/G or G/C versus C/C at 440 (adjusted OR=5.8; 95% CI, 1.56–21.3; P=0.009) of the UGT1A-3′-UTR as independent risk factors for nephrolithiasis (Table 4).

Table 3. Univariate analysis to estimate the association of various factors with atazanavir-induced nephrolithiasis

	OR	95% CI	*P* value
Male	1.7	0.31–9.51	0.53
Age per year	1.0	0.93–1.03	0.39
Weight per 1 kg increment	1.0	0.95–1.03	0.60
BMI per 1 kg/m^2 increment	1.0	0.83–1.11	0.58
CD4 count per 1 cell/mm^3 increment	1.0	1.00–1.00	0.63
Baseline eGFR per 1 mL/min/1.73 m^2 decrement	1.0	0.98–1.03	0.80
HIV-1 viral load per 1 $\log_{10}$/mL increment	0.9	0.62–1.34	0.64
Hepatitis C infection	8.8	0.98–79.9	0.052
Hepatitis B infection	1.5	0.09–25.5	0.77
Treatment naive	0.7	0.25–1.66	0.37
History of nephrolithiasis	3.3	0.57–19.4	0.18
Uric acid per 1 mg/dL increment	1.2	0.93–1.56	0.16
Hypertension	0.7	0.17–3.17	0.68
Diabetes mellitus	0.8	0.07–8.64	0.82
Co-administration of tenofovir	0.7	0.27–1.92	0.51
History of indinavir use	1.6	0.30–8.34	0.60
ABCB1			
193 A/A versus A/G or G/G	0.8	0.32–1.97	0.61
365 T/T versus T/C or C/C	2.5	0.63–10.0	0.19
1236 C/C versus C/T or T/T	0.7	0.22–2.33	0.57
2677 T/T versus T/A or G/G or G/T or G/A or A/A	1.6	0.43–6.12	0.48
3435 T/T versus T/C or C/C	2.1	0.51–8.40	0.31
NR1I2			
131 A/A versus A/C or C/C	1.0	0.40–2.58	0.97
370 G/G versus G/A or A/A	0.7	0.25–1.84	0.44
522 C/C versus C/T or T/T	0.7	0.27–2.04	0.56
1195 C/C versus C/A or A/A	0.7	0.30–2.27	0.70
1232 C/C versus C/T or T/T	0.7	0.25–1.84	0.44
44477 C/C versus C/T or T/T	1.1	0.42–2.67	0.89
63396 C/C versus C/T or T/T	2.2	0.45–10.5	0.33
UGT1A1			
211 G/G versus G/A or A/A	0.9	0.35–2.29	0.82
c.211 T/C versus C/C	3.8	1.22–11.6	0.022
339 G/C versus C/C	5.9	1.68–20.9	0.006
440 G/G or G/C versus C/C	5.9	1.68–20.9	0.006
UGT1A1 *28/*28 or *28/*1 versus *1/*1	2.2	0.45–10.5	0.33
SLCO1B1			
388 G/G versus G/A or A/A	1.6	0.30–8.34	0.60
521 T/T versus T/C or C/C	0.9	0.36–2.43	0.90
CYP3A5			
14 T/T versus T/C or C/C	0.9	0.38–2.33	0.89

Discussion

To our knowledge, this is the first study that has elucidated the association between genetic polymorphisms in the genes encoding proteins that affect atazanavir exposure and atazanavir-induced nephrolithiasis. The results demonstrated that Japanese HIV-1-infected patients who developed atazanavir-induced nephrolithiasis were ~5-fold more likely to have variants in the UGT1A-3′-UTR, compared with those without nephrolithiasis, who were well-matched for other traditional risk factors for nephrolithiasis. These findings suggest a link between genetic factors and nephrolithiasis, a major adverse event of atazanavir that can significantly affect renal function. On the other hand, the results showed no association between variants in *ABCB1* and *SLCO1B1*, the genes that encode drug transporter protein for atazanavir, *CYP3A5*, the main metabolizer of atazanavir, and *NR1I2*, which encodes PXR to regulate the expression of metabolizers and transporters of atazanavir, and atazanavir-induced nephrolithiasis.

This study enrolled only Japanese patients in order to examine a population with comparatively similar genetic backgrounds. It is possible that the association of UGT1A-3′-UTR variants with atazanavir-induced nephrolithiasis could be more significant in people of African or European origin than Japanese or East Asians, considering that the allele frequencies of these variants are higher in these populations according to the HapMap data [e.g. minor allele frequency at position 440 (rs8330): Africans 50%, Europeans 23.3%, Japanese 15.9%, Chinese 15.6%] (www.hapmap.org). Similar studies are needed in these populations to confirm that the association between UGT1A-3′-UTR variants and atazanavir-induced nephrolithiasis is reproducible.

The mechanism by which SNPs in the UGT1A-3′-UTR are associated with the development of nephrolithiasis in patients on an atazanavir-containing regimen is unknown. However, Court

Table 4. Multivariate analysis to estimate the association of SNPs of the UGT1A-3′-UTR with atazanavir-induced nephrolithiasis

UGT1A-3′-UTR	Adjusted OR	95% CI	*P* value
Genotype T/C versus C/C at position c.211	3.7	1.13–11.9	0.030
Genotype G/C versus C/C at position 339	5.8	1.56–21.3	0.009
Genotype G/G or G/C versus C/C at position 440	5.8	1.56–21.3	0.009

Each SNP was tested in the model separately.
Each variable was adjusted for sex, age and hepatitis C infection.

et al.[32] reported that these SNPs are associated with inter-individual variability in acetaminophen (paracetamol) glucuronidation in the human liver, and provide protection against acute liver failure by acetaminophen overdose, probably through more extensive detoxification of acetaminophen via glucuronidation. Because the biotransformation pathways of atazanavir or its metabolites also include glucuronidation,[12] the UGT1A-3′-UTR variants could alter atazanavir metabolism and pharmacokinetics, resulting in increased atazanavir concentration in the blood and increased excretion in urine, facilitating nephrolithiasis formation. Unfortunately, serum and urine concentrations of atazanavir were not measured in the present study. It is also notable that the *UGT1* subfamily has a unique gene structure; the *UGT1* gene has 13 exon 1s from *UGT1A1* to *UGT1A13P*, and exons 2–5, which are common in all mRNAs expressed from the gene.[36] The UGT1A-3′-UTR is located in exon 5, which is commonly present in the UGT1 subfamily (Figure 1), and thus the variants in the UGT1A-3′-UTR might influence not only UGT1A1 but also other UGT1 isoforms that take part in glucuronidation of various substrates,[36] and they might affect atazanavir metabolism and pharmacokinetics as well. Figure 1 also shows that the identified SNPs in the UGT1 3′-UTR are in tight linkage disequilibrium with the gene next to them (*HEATR7B1*), suggesting that the latter could also affect atazanavir metabolism/transportation. To our knowledge, however, there is no information on the role of *HEATR7B1* in drug metabolism/transportation, and the above conjecture remains to be investigated.

In this study, the median serum total bilirubin level in the case patients was higher than that in the control group. Rockwood *et al.*[8] reported a close relationship between hyperbilirubinaemia and the development of atazanavir-induced renal stones. However, no such relationship was found in our previous cohort study.[6] In two pharmacokinetics studies, Rodríguez-Nóvoa *et al.*[20,29] reported that serum bilirubin level correlated with plasma atazanavir concentration, and one can speculate that high bilirubin levels might reflect higher atazanavir concentrations, which result in precipitation of atazanavir in urine and renal stone formation. However, these results are still preliminary and further studies are needed to determine the true relationship between serum bilirubin level and atazanavir-related nephrolithiasis.

Several limitations of this study need to be acknowledged. First, and importantly, although this study identified association between the UGT1A-3′-UTR variants and atazanavir-induced nephrolithiasis, the number of enrolled patients was small in this case–control study; the results need to be interpreted with caution. The results could provide the basis for an exploratory hypothesis and further larger studies are needed to confirm such an association. Second, not all polymorphisms in genes of the targeted proteins were examined. Thus, we might have missed other important SNPs associated with or affecting the metabolism or transportation of atazanavir. There might be other, unknown proteins that take part in the metabolism or transportation of atazanavir that also contribute to susceptibility to atazanavir-induced nephrolithiasis. Third, because renal stone formation occurs as a composite of various factors and the components of nephrolithiasis were not analysed in the study, it is difficult to exclude the effects of classic risk factors for renal stone formation, apart from the genetic factors identified in the present study. However, the two study samples were well matched in terms of risk factors, such as BMI, serum uric acid and history of indinavir use.[4,5,24–26] Furthermore, the susceptibility to nephrolithiasis in patients on an atazanavir/ritonavir-containing regimen is well established; the incidence of nephrolithiasis is 10- to 20-fold higher in patients on atazanavir/ritonavir-containing ART than in patients on other protease inhibitor-containing ART regimens.[6,7] Fourth, because functional data are not yet available, clinical or biochemical studies to confirm the results obtained here are certainly needed. We did not measure atazanavir concentration in blood or urine.

In conclusion, in a setting where other predisposing factors for nephrolithiasis were well matched, the present study demonstrates that the Japanese HIV-1-infected patients who developed atazanavir-induced nephrolithiasis were ~5-fold more likely to have variants in the UGT1A-3′-UTR compared with those without nephrolithiasis. Further studies are warranted to confirm this association and to elucidate how these SNPs might influence the metabolism and excretion of atazanavir and the formation of nephrolithiasis.

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Brain Magnetic Resonance Imaging Screening Is Not Useful for HIV-1-Infected Patients Without Neurological Symptoms

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Abstract

We investigated the diagnostic usefulness of brain magnetic resonance imaging (MRI) screening in HIV-1-infected patients without neurological symptoms in detecting intracranial diseases at early stages. In this retrospective analysis, the study patients were HIV-1-infected patients who underwent brain MRI scan in clinical practice between 2001 and 2013. We excluded patients with MRI for (1) follow-up examination for prediagnosed intracranial diseases, (2) cancer staging, (3) screening mycobacterium/bacteria/fungi disease proliferation in the brain, and (4) evaluation for meningitis/encephalitis. The study patients ($n=485$) were classified into two groups: those who underwent brain MRI scan without any neurological symptoms/signs (asymptomatic patients, $n=158$) and those who underwent MRI due to such symptoms (symptomatic patients, $n=327$). Asymptomatic patients had lower CD4 counts than symptomatic patients (median 78 versus 241/μl). Intracranial diseases were detected in three (2%) of the asymptomatic patients [two toxoplasmosis and one progressive multifocal leukoencephalopathy (PML)] compared to 58 (19%) of the symptomatic patients (the χ^2 test, $p<0.01$). The latter included toxoplasmosis ($n=10$), PML ($n=7$), cytomegalovirus encephalitis ($n=3$), primary central nervous system lymphoma ($n=3$), cryptococcoma/meningitis ($n=3$), and HIV-associated dementia ($n=17$). Among symptomatic patients, intracranial diseases were common in those with slurred speech (3/6, 50%), seizure (4/10, 40%), eyesight/vision abnormality (5/16, 31%), altered mental status (8/31, 26%), and hemiplegia/numbness (13/50, 26%). For patients with CD4 count $<200/\mu$l, intracranial diseases were detected in only 3 (3%) of 144 asymptomatic patients, compared with 46 (32%) of 113 symptomatic patients ($p<0.01$). Brain MRI screening for HIV-1-infected patients without neurological symptoms is of little value.

Introduction

PATIENTS WITH ADVANCED HIV-1 INFECTION are prone to develop intracranial opportunistic diseases, such as toxoplasma encephalitis, primary central nervous system lymphoma (PCNSL), progressive multifocal leukoencephalopathy (PML), and cytomegalovirus (CMV) encephalitis.[1] Although the introduction of antiretroviral therapy (ART) substantially decreased the incidence of neurological opportunistic infections,[2,3] such diseases have high associated mortality even with appropriate treatment, and recurrences and residual neurological deficits can occur.[4,5] Because delayed diagnosis of these intracranial diseases has a detrimental effect on patients with HIV-1 infection,[5,6] early diagnosis, not to mention prevention, of such diseases is of importance.

Brain magnetic resonance imaging (MRI) is often preferred to computed tomography (CT) in establishing the diagnosis of many of these diseases due to its superior sensitivity to subtle white matter and meningeal disease.[7–10] However, there is no information on the utility of brain MRI screening for HIV-1-infected patients without neurological symptoms/signs in detecting intracranial opportunistic diseases at early stages. This observational study was designed to assess the usefulness of brain MRI screening of such patients with HIV-1 infection.

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Materials and Methods

Study design, setting, and participants

We conducted an observational single-center study to investigate the usefulness of brain MRI screening in HIV-1-infected patients without neurological symptoms who warrant investigation for intracranial diseases. The study was conducted at the AIDS Clinical Center, National Center for Global Health and Medicine (NCGM), Tokyo, the largest referral center for HIV care in Japan.[11] The study patients were those who fulfilled the following inclusion criteria: HIV-1-infected patients who underwent brain MRI scan in clinical practice between June 2001 and August 2013. In addition, the following exclusion criteria were applied: patients who underwent brain MRI for (1) follow-up examination during the study period because of intracranial diseases such as opportunistic infections, stroke, or malignancy, which were diagnosed prior to the referral to our clinic, (2) staging of malignant tumors, (3) screening mycobacterium/bacteria/fungi disease proliferation in the brain in patients who were already diagnosed with mycobacterial diseases or bacteremia or fungemia, and (4) evaluation of meningitis/encephalitis.

The study patients ($n=485$) were classified into those who underwent brain MRI scan without any neurological symptoms, such as seizure, altered mental status, hemiplegia/numbness, headache, or fever (asymptomatic patients, $n=158$), and those who underwent MRI due to the abovementioned symptoms, which can suggest a focal brain lesion[5] (symptomatic patients, $n=327$). Asymptomatic patients included those who underwent MRI due to positive antitoxoplasma IgG antibody ($n=38$) and positive serum cryptococcal antigen ($n=1$). At our clinic, patients with a low CD4 cell count (typically less than 200/μl) often underwent brain MRI even though they had no neurological symptoms/signs that would warrant a brain imaging examination to rule out intracranial opportunistic infections or malignancy at early stages.

The study was approved by the Human Research Ethics Committee of NCGM. All patients included in this study provided written informed consent for their clinical and laboratory data to be used and published for research purposes. The study was conducted according to the principles expressed in the Declaration of Helsinki.

Measurements

At our hospital, brain MRI was routinely read by one experienced radiologist and the findings were confirmed by another radiologist. Furthermore, the MRI diagnosis was confirmed by reviewing the medical records and follow-up brain imaging when available. The diagnostic criteria for cryptococcal meningitis, cytomegalovirus encephalitis, and toxoplasmic encephalitis were those adopted by the AIDS Clinical Trials Group (ACTG)-A5164.[12] HIV-associated dementia in this study was diagnosed based on the MRI findings, which included generalized atrophy and prominent white matter changes plus cognitive impairment based on the chart review, and not necessarily required neurocognitive function tests.[8] The reasons for conducting an MRI were also extracted from the medical records. Baseline characteristics and HIV-1-related variables at the time of brain MRI were also extracted from the medical records. They included age, sex, ethnicity, history of AIDS, route of HIV-1 transmission, treatment status for HIV-1 infection (either treatment naive or experienced), CD4 cell count, and HIV viral load. For CD4 count and HIV load, we used data collected closest to and preceding by up to 3 months the day of the brain MRI. In Japan, because the prescription period under the health care system is limited to 3 months, patients need to visit the HIV Clinic at least once every 3 months for prescriptions as well as monitoring CD4 cell count and HIV-1 load.[11]

Statistical analysis

Baseline characteristics were compared between asymptomatic and symptomatic patients using the Student's t-test and χ^2 test (Fisher's exact test) for continuous and categorical variables, respectively. Prevalence of intracranial diseases was calculated among asymptomatic patients and compared to that of symptomatic patients with the χ^2 test. The logistic regression model was used to estimate the associations of lack of neurological symptoms/signs over the presence of such symptoms/signs with the MRI findings of intracranial diseases. The model was adjusted for age, sex, CD4 count, HIV treatment status, and history of AIDS. Subgroup analysis included the prevalence of intracranial diseases in patients with a CD4 count $<200/\mu$l. Statistical significance was defined as two-sided p values <0.05. We used odds ratios (ORs) with 95% confidence intervals (95% CIs). All statistical analyses were performed with The Statistical Package for Social Sciences ver. 21.0 (SPSS, Chicago, IL).

Results

The study included 485 patients who underwent a brain MRI scan in clinical practice, of whom 158 had no neurological symptoms (asymptomatic) and 327 did have such symptoms (symptomatic). Of the total patients, 475 (98%) were Asians, 446 (92%) were males, and 365 (75%) were infected with HIV-1 through homosexual contact (Table 1). The median age of the study patients was 41 [interquartile range (IQR) 34–51]. Asymptomatic patients had a lower CD4 count [median 78/μl, interquartile range (IQR) 21–237, symptomatic: 241/μl, 60–470 ($p<0.01$)] and higher HIV-1 viral load [4.84 $\log_{10}$/ml, IQR 2.97–5.62, symptomatic: 2.95 $\log_{10}$/ml, 1.70–5.11 ($p<0.01$)] than symptomatic patients. Asymptomatic patients were more likely to be treatment naive (68% versus 41%, $p<0.01$) and have a history of AIDS (62% versus 47%, $p<0.01$). There was no significant difference in other baseline characteristics between the two groups (Table 1).

Among the 158 asymptomatic patients, brain MRI screening detected toxoplasmosis ($n=2$) and PML ($n=1$, with CD4 43/μl), i.e., a prevalence of intracranial diseases of 2%. The two patients with toxoplasmosis underwent brain MRI due to positive antitoxoplasma IgG antibody with a titer of 20,480 (CD4 168/μl) and 1,280 (CD4 16/μl) IU/ml. In asymptomatic patients who underwent brain MRI due to positive antitoxoplasma IgG antibody, intracranial diseases were detected in 3 (8%) out of 38 patients (Table 2). On the other hand, brain MRI for symptomatic patients detected 58 intracranial diseases with a prevalence of 19%. The cases included toxoplasmic encephalitis ($n=10$), PML ($n=7$), CMV encephalitis ($n=3$), PCNSL ($n=3$), cryptococcosis/meningitis ($n=3$), herpes simplex virus encephalitis ($n=1$), HIV-associated dementia ($n=17$), acute cerebral infarction ($n=8$), gummatous

TABLE 1. CLINICAL CHARACTERISTICS OF THE STUDY PATIENTS ACCORDING TO NEUROLOGICAL SYMPTOMS

	All patients (n=*485*)	*Patients without neurological symptoms* (n=*158*)	*Patients with neurological symptoms* (n=*327*)	p *value*
Male sex, *n* (%)	446 (92)	146 (92)	300 (92)	0.86
Age[†]	41 (34–51)	42 (33–52)	41 (35–49)	0.95
Asian, *n* (%)	475 (98)	154 (98)	321 (98)	0.74
CD4 cell count (/μl)[a]	178 (41–420)	78 (21–237)	241 (60–470)	<0.01
HIV-1 load (log_{10}/ml)[a]	4.20 (1.70–5.26)	4.84 (2.97–5.61)	2.95 (1.70–5.11)[b]	<0.01
Homosexual contact, *n* (%)	364 (75)	117 (74)	247 (76)	0.74
Treatment naive, *n* (%)	240 (50)	107 (68)	133 (41)	<0.01
History of AIDS, *n* (%)	250 (52)	98 (62)	152 (47)	<0.01

[a]Median (interquartile range).
[b]Data on HIV-1 load are not available for two patients.

syphilis ($n=1$), tuberculoma ($n=1$), metastatic cancer ($n=1$), chronic subdural hematoma ($n=1$), schwannoma ($n=1$), and progressive supranuclear palsy ($n=1$) (Table 2). In asymptomatic patients, intracranial diseases were less likely to be detected by brain MRI, compared to symptomatic patients [by univariate and multivariate analysis (OR=0.1; 95% CI, 0.03–0.29; $p<0.01$) (adjusted OR=0.1; 95% CI, 0.02–0.17; $p<0.01$)]. Patients with higher CD4 counts were also less likely to have intracranial diseases (per 100/μl increment, adjusted OR=0.7; 95% CI, 0.55–0.83; $p<0.01$). Among the symptomatic patients, those who presented with slurred speech, seizure, eyesight/vision abnormality, altered mental status, and hemiplegia/numbness were highly likely to have intracranial diseases, with a prevalence of 50%, 40%, 31%, 26%, and 26%, respectively (Table 3).

Subgroup analysis limited to data of patients with CD4 count of <200/μl showed that the abovementioned three intracranial diseases were detected in 144 asymptomatic patients with a prevalence of 3%, compared to 46 (32%) of 113 symptomatic patients (asymptomatic over symptomatic, OR=0.1; 95% CI, 0.02–0.19; $p<0.01$) (Table 2). Only a few intracranial opportunistic diseases were diagnosed in patients with a CD4 count of ≥200/μl; PCNSL ($n=1$), HIV-associated dementia ($n=4$), acute cerebral infarction ($n=6$), metastatic cancer ($n=1$), and progressive supranuclear palsy ($n=1$).

Discussion

In this observational study of patients who underwent brain MRI screening in clinical practice, only 2% of patients without neurological symptoms/signs that warranted investigation of intracranial diseases were found to have intracranial diseases, whereas a significantly higher prevalence (19%) of intracranial diseases was detected in patients who underwent brain MRI due to such symptoms. Among patients with a CD4 count of <200/μl, who are reported to be at high risk for intracranial diseases,[5,10] the result was similar; 3% and 32% of asymptomatic and symptomatic patients, respectively, were found to have intracranial diseases. On the other hand, high detection rates of intracranial diseases by brain MRI were observed in patients who presented with slurred speech (50%), seizure (40%), eyesight/vision abnormality (31%), altered mental status (26%), and hemiplegia/

TABLE 2. PREVALENCE OF INTRACRANIAL DISEASES DETECTED BY BRAIN MAGNETIC RESONANCE IMAGING ACCORDING TO NEUROLOGICAL SYMPTOMS

Intracranial diseases	*Patients without neurological symptoms* (n=*158*)	*Patients without neurological symptoms with CD4 <200/μl* (n=*144*)	*Patients with neurological symptoms* (n=*327*)	*Patients with neurological symptoms with CD4 <200/μl* (n=*113*)	*Positive toxoplasma Ab and without neurological symptoms* (n=*38*)
Toxoplasmosis	2 (1)	2 (2)	10 (3)	10 (7)	2 (1)
PML	1 (1)	1 (1)	7 (2)	7 (5)	1 (1)
HIV-associated dementia			17 (6)	13 (9)	
Malignant lymphoma			4 (1)	3 (2)	
CMV encephalopathy			3 (1)	3 (2)	
Cryptococcoma/meningitis			3 (1)	3 (1)	
HSV encephalopathy			1	1	
Gummatous syphilis			1	1	
Tuberculoma			1	1	
Metastatic cancer			1		
Cerebral infarction			8 (3)	2 (1)	
Others			3 (1)	2 (1)	
Total	3 (2)	3 (3)	59 (19)	46 (32)	3 (8)

Data are numbers (percentages) of patients.
Ab, antibody; PML, progressive multifocal leukoencephalopathy; CMV, cytomegalovirus; HSV, herpes simplex virus.

TABLE 3. PREVALENCE OF INTRACRANIAL DISEASES DETECTED BY BRAIN MAGNETIC RESONANCE IMAGING ACCORDING TO NEUROLOGICAL SYMPTOM CATEGORIES

	Intracranial diseases	*Prevalence of intracranial diseases*
Slurred speech ($n=6$)	Cerebral infarction $n=2$ PML $n=1$	50%
Seizure ($n=10$)	Toxoplasmosis $n=2$ PML $n=1$ HSV encephalitis $n=1$	40%
Eyesight/vision abnormality ($n=16$)	Malignant lymphoma $n=2$ HIV-associated dementia $n=2$ Metastatic cancer $n=1$	31%
Altered mental status ($n=31$)	Toxoplasmosis $n=2$ HIV-associated dementia $n=2$ Cryptococcoma/meningitis $n=2$ PML $n=1$ Tuberculoma $n=1$	26%
Hemiplegia/numbness ($n=50$)	Cerebral infarction $n=5$ Toxoplasmosis $n=3$ PML $n=3$ HIV-associated dementia $n=1$ Other $n=1$	26%
Neurocognitive impairment ($n=62$)	HIV-associated dementia $n=9$ Cerebral infarction $n=1$ CMV encephalitis $n=2$	19%
Fever work-up ($n=12$)	Malignant lymphoma $n=1$ HIV-associated dementia $n=1$	17%
Dizziness/vertigo/tinnitus ($n=45$)	Toxoplasmosis $n=1$ PML $n=1$ Malignant lymphoma $n=1$ HIV-associated dementia $n=1$ CMV encephalitis $n=1$	11%
Abnormal ophthalmologic examination ($n=11$)	HIV-associated dementia $n=1$	9%
Headache ($n=49$)	Toxoplasmosis $n=2$	4%
Syncope ($n=16$)		0%

PML, progressive multifocal leukoencephalopathy; HSV, herpes simplex virus; CMV, cytomegalovirus.

numbness (26%). The present study indicates that brain MRI screening for HIV-1-infected patients without neurological symptoms/signs, even those with a low CD4 count (< 200/μl), is of little value. In contrast, MRI screening is useful for patients with particular neurological symptoms/signs. These findings can help reduce unnecessary brain MRI examinations and can be helpful in clinical decision making.

Interestingly, in both of the two asymptomatic toxoplasmic encephalitis patients who underwent brain MRI screening because of positive antitoxoplasma IgG antibody, the antibody titer was very high (20,480 IU/ml and 1,280). Together with the fact that the prevalence of intracranial diseases in asymptomatic patients with positive antitoxoplasma IgG antibody was higher (8%) than the 2% in the entire group of asymptomatic patients, brain MRI screening for patients without neurological symptoms/signs who presented with high antitoxoplasma antibody may be of value and clinically justifiable.

Our study has certain limitations. First, because brain MRI was performed at the discretion of the treating physician, patient selection bias, especially among those without neurological symptoms/signs, cannot be ruled out. However, we had a large number of study patients, and considering the availability and cost of an MRI scan, the results of the present study are of value and are useful in clinical decision making. Second, because endemic opportunistic infections vary depending on the region[13,14] and the majority of our patients were Asian, the results of the present study might not be applicable to patients in other regions. Third, in this study the diagnosis of HIV-associated dementia was based on the MRI findings plus cognitive impairment based on a chart review, and the patients did not necessarily undergo neurocognitive function tests.[8] This is because the present study included patients from 2001, long before the diagnostic Frascati criteria for an HIV-associated neurocognitive disorder that required neurocognitive function tests were established.[15]

In conclusion, although our results suggest that brain MRI screening is of little value in HIV-1-infected patients without neurological symptoms/signs that warrant investigation on intracranial diseases, it should be performed in HIV-1-infected patients who present with particular neurological symptoms, such as slurred speech and seizure.

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Author Disclosure Statement

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厚生労働科学研究費補助金エイズ対策研究事業

多剤耐性 HIV 変異株に強力で高い中枢神経系透過性を有する新規抗 HIV 薬の開発
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