Review

Hepatitis G Virus: Molecular Organization, Methods of Detection, Prevalence, and Disease Association

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ABSTRACT

This article reviews data on hepatitis G virus (HGV) prevalence and possible disease associations in various groups of patients. An important fraction of acute or chronic hepatitis cases probably have a viral etiology and are not attributable to known hepatitis viruses. Therefore, researchers continually are looking for new hepatitis viruses. Among the agents found are members of GB hepatitis viruses, including GB-C virus, or HGV. This review presents the history of the discovery of HGV, its molecular biology and some methods of detection; results of clinical and molecular studies of HGV infection also are discussed.

Key Words: *flaviviruses, hepatitis, hepatitis G virus, methods of virus detection, risk groups, routes of transmission*

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About 10 to 15% of sporadic and 15 to 20% of non-A-E post-transfusion hepatitis cases probably have a viral etiology and are not attributable to known hepatitis viruses. In 1995 and 1996, two independent research groups described new viruses, named GBV-C and hepatitis G virus (HGV) respectively, that were detected in sera obtained from non-A-E hepatitis patients. Comparisons of nucleotides and amino acid sequences of the viruses revealed that they were isolates of the same virus. The name of the virus has not yet been chosen and the HGV nomenclature will be used throughout this article.

The relation between the newly described virus infection and human pathology has not yet been established. There are conflicting results and more research must be carried out to determine whether HGV is a human pathogen. Numerous recent editorials, comments, and reviews deal with the problems of molecular characterization, diagnosis, prevalence, and pathogenicity of HGV.[1–9] In this review, the published methods of HGV detection, as well as the results of clinical and molecular studies on HGV infection are described.

DISCOVERY OF GBV-A, GBV-B, AND HGV (GBV-C)

GB agent hepatitis originally was described by Deinhardt et al,[10] who inoculated tamarins (*Saquinus* sp) with the serum of a surgeon with the initials "G.B." Both the animals inoculated directly with the GB serum and those inoculated with serum from tamarins with acute phase hepatitis, after subsequent serial passages, developed hepatitis. A modified version of the polymerase chain reaction (PCR) technique known as representational difference analysis (RDA) was used to clone specific nucleotide sequences present in the infectious plasma from tamarins.[11] This led to the identification of two RNA viruses, GB virus A (GBV-A) and GB virus B (GBV-B), which possessed limited sequence identity to each other and to members of the hepatitis C virus (HCV) group of the *Flaviviridae*.[12] Both GBV-A and GBV-B probably cause hepatitis in tamarins,[7,13] but many New World monkeys are persistently infected with GBV-A-like viruses, and no signs of disease are associated with chronic infection.[14]

Subsequent testing by reverse transcript PCR (RT-PCR) of sera from humans who possessed antibodies to recombinant proteins from GBV-A and GBV-B revealed the presence of a third, novel RNA virus, GBV-C.[15] Reverse transcript PCR was performed with degenerate primers capable of amplifying a segment of the conserved helicase region from GBV-A, GBV-B, or HCV-1.

Independent research by Linnen et al led to the isolation of a novel virus termed the hepatitis G virus (HGV).[16] Whole RNA extracted from the serum of a patient with non-A-B hepatitis was reverse transcribed with random primers and subsequently amplified by sequence-independent single-primer amplification. Products of amplification were cloned and a single colony of

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an expression library, reactive with the serum of the patient, was identified. Multiple overlapping cDNA clones were generated from the colony by an anchored PCR. The sequences of the clones were combined to create HGV genome. Nucleotide and amino acid sequence analysis of HGV and GBV-C revealed that they are separate isolates of the same virus. Some full-length or nearly full-length HGV genome sequences have been determined, and the genome data are described according to these study results.[16-19]

GENOME STRUCTURE

Flaviviruses are enveloped viruses that contain a single positive-sense genomic RNA molecule of about 10 kb. The length and the position of the structural and nonstructural genes of the GBV-A, GBV-B, and HGV viruses are similar to other members of the *Flaviviridae* (Table 1).

Genes predicted to encode structural (E1, E2) and nonstructural (NS2, NS3, NS4, NS5A, NS5B) proteins are located at the 5′ and 3′ ends respectively.[12,17] The genes coding for nonstructural proteins of the GB and HGV viruses appear to be similar to HCV and other members of the *Flaviviridae*, whereas the genes coding for structural proteins have similarities and numerous differences.

5′ Untranslated Regions

The 5′ termini of the GB, HGV, and HCV virus genomes represent untranslated regions (UTRs). GBV-A and HGV contain large 5′ UTRs that have limited sequence identity to each other but no identity with either HCV and GBV-B.[17] However, the GBV-B 5′ UTR appears similar to the HCV and other flaviviruses in conserved sequences and in closely related RNA secondary structures within 5′ UTR.[12,20] In this region of HGV, four highly conserved domains were found, suggesting a crucial role for the region in viral replication or gene expression.[21] About 90% of sequence homology within 5′ UTRs is maintained among the isolates from the different geographic areas.[22] Recently, Hsieh et al detected a potential hairpin structure also in the 5′ end of the noncoding region of HGV.[22]

3′ Untranslated Region

The 3′ ends of these viruses represent the untranslated regions (UTRs). In general, the positive-strand RNA viruses conclude with a poly-(A) tract, whereas HCV concludes with either poly-(A) or a poly-(U) tracts.[23-25] GBV-B is unique; it contains an additional 50 nucleotides downstream from a poly-(U) tract.[12] The sequence of the GBV-A 3′ UTR possesses a sequence of 35 nucleotide; however, no poly-(U) or poly-(A) tracts were identified.[12] Experiments on HGV 3′ UTR have failed to identify either poly-(U) or poly-(A) sequences.[17] In this regard, HGV closely resembles GBV-A.

Table 1. Comparision of Some Genome Elements and Occurrence in Human of the GB Viruses and Hepatitis G and C Viruses

Parameter	*GBV-A*	*GBV-B*	*HGV*	*HCV*
Whole genome length (nt)	9653	9143	9103–9395	9401
5′ UTR (nt)	594	445	281–551	341
3′ UTR (nt)	198	83	313–315	72
Polyprotein (aa)	2954	2864	2842–2933	3011
Presence of basic core protein	–	+	–	+
Occurrence in humans	–	–	+	+

nt = nucleotide; aa = amino acid; UTR = untranslated regions. (Adapted from Simons et al[7] and Linnen et al.[18])

GENE PRODUCTS

GB viruses and HCV are similar in size and structure. Each possesses single, large, open reading frames encoding putative polyproteins of about 3000 amino acid residues. The structural proteins are positioned in the N-terminal third of the polyprotein, whereas the nonstructural proteins are in the C-terminal two-thirds of the polyprotein.[7]

Structural Proteins

GBV-B and HCV appear to encode a small (156 and 191 amino acids, respectively), strongly basic protein (pI 11.1 and 11.9), presumed to be the nucleocapsid or core, at the N-terminus of the polyprotein. Two putative envelope glycoproteins (E1 and E2) with several potential N-linked glycosylation sites are located downstream of the core.[12] These structural proteins appear in all members of the *Flaviviridae* examined to date.[26,27]

GBV-A and HGV also encode two putative envelope proteins that contain relatively few potential N-linked glycosylation sites, but these viruses appear unique among members of the *Flaviviridae* in that they do not encode a basic core protein upstream of the viral glycoproteins.[7] It is possible that the capsid protein is provided by an as yet unidentified helper virus or by a cellular protein that plays the role of a capsid protein.[5] In both of these viruses the initiator AUG codon is located immediately upstream of the putative E1 envelope signal sequence and may function as an internal ribosome entry site.[28]

Nonstructural Proteins

Amino acid sequence alignments with other members of the *Flaviviridae* suggest that the GB viral genomes encode supergroup II RNA helicases and supergroup II RNA-dependent RNA polymerases. In addition, sequence motifs consistent with virus-encoded proteases and protease cleavage sites are found in each of these viruses,[12,17] predicting that every GB virus encodes five nonstructural proteins: NS2, NS3, NS4, NS5A, NS5B.

GB viruses and HCV have two proteases, one in NS2 and a portion of NS3 that is believed to be involved in autocatalytic cleavage at the NS2–NS3 junction, and the other, a chymotrypsin-like serine protease located within the N-terminal one-third of NS3 that is responsible for processing of the downstream nonstructural proteins at specific recognition sites. HGV NS3-encoded serine protease, despite low sequence homology (about 30%), shares substrate specificity with the HCV NS3 protease.[29] It is presumed that in GB viruses such as those in HCV, host and viral proteases are responsible for processing of the structural and nonstructural proteins respectively.[12,17] As was observed for flavi-like viruses,[30] the greatest region of identity occurs within helicase area NS3.

Within the putative NS5B region, a number of residues conserved in the supergroup II replicases of positive-strand RNA viruses are maintained in HGV.[17,30] GBV-A and GBV-B also possess many of the conserved residues, however, there are some significant differences.[12]

The functional role of the HCV NS4 and NS5A proteins is unknown; however, based on the regional sequence identity between HCV and GB viruses, these proteins can be expected to perform similar functions.

HEPATITIS G VIRUS SUBTYPES

The mutation rate of HGV is relatively low. During 8.4 years of observation of virus isolates from one patient, 3.9×10^{-4} base substitutions per site per year were estimated.[31] Therefore, HGV appeared to be significantly less variable than HCV.[32] Nevertheless, recent studies reported HGV strains with low sequence identity with previously reported isolates.[33] They were detected mainly in Japanese patients, and it seemed that some HGV isolates should be placed in new genotypes.[33] Hepatitis G virus isolates from China were reported to be more similar to Japanese isolates than to isolates from the United States and Africa.[34] In Nicaraguan patients the high prevalence of HGV strains related to those of Asian origin was detected.[35] Muerhoff et al and Mukaide et al described three groups of HGV sequences based on heterogeneity within a 5′-terminal sequence.[36,37] The existence of two different subtypes of HGV in Italy has been suggested,[38] the Taiwanese and Japan isolates have been classified into three groups,[39,40] and the Mongolian isolates into two types.[41] Okamoto et al divided HGV isolates into three genotypes, tentatively designated G1, G2, and G3.[19] These data suggest that HGV isolates cloned from different geographic areas have genetic heterogeneity. However, Pickering et al reported only one level of variation within HGV sequences, in contrast to three distinct ranges corresponding to isolate, subtype, and genotype levels of variations in HCV, and argued against these divisions in HGV.[32] Smith et al discriminated geographic variants of HGV by analysis of the 5′ noncoding region, and they stated that the low level of amino acid sequence variation observed between groups of variants suggested that they are unlikely to display significant biologic differences.[42]

DETECTION OF HEPATITIS G VIRUS

Detection of Hepatitis G Virus RNA

Detection of HGV genomic RNA in human serum, plasma, or cellular samples relies on the RT-PCR assays, which use oligonucleotide primers that amplify the NS3 helicase domain or highly conserved regions within the 5′ UTR.[43,44]

The NS3-based method uses degenerate oligonucleotide primers designed to the most highly conserved sequences of helicase domain, the amplification being performed by "touchdown PCR," which allows specific product amplification despite small primer-template mismatches that may be present.[45] The detection of specific PCR relies on Southern hybridization.[43] The second-round of PCR can be carried out with nested primers.[46] Yoshiba et al described the seminested PCR, using a combination of the sense primer and two antisense primers for amplification of a 140-bp fragment from the conserved helicase region of HGV.[47]

The 5′ UTR-based method avoids the use of degenerate primers as 5′ UTR possesses a high sequence conservation among the isolates.[44] A standard thermocycling protocol is used for amplification. Detection is based on Southern hybridization or PCR enzyme-linked immunosorbent assay (ELISA) digoxygenine labelling and detection system (Boehringer Mannheim, Sydney).[48]

Kao et al compared sensitivity and specificity of PCR assays using primers from different regions of the viral genome: 5′ UTR, E2, and NS3.[49] The positive rates by 5′ UTR, NS3, and E2 primers were 100%, 98%, and 84%, respectively, and the sensitivity of PCR assays using 5′ UTR primers happened to be 10 to 100 times more likely to detect HGV RNA than that of NS3 and E2 primers. Bhardwaj et al, Cantaloube et al, and Zhang et al reached similar conclusions.[50–52]

There also are primers targeting the NS5B replicase region of HGV (Genelabs Technologies Inc., USA; Boehringer Mannheim, Germany), and such a PCR product is detected by dot blot hybridization using a riboprobe or enzyme-linked test (Semiquantitative Enzymun-Test).[48,53] Schlueter et al also propose the amplification by PCR of two independent regions of the viral genome: 5′ UTR and NS5A.[53] They demonstrated the increased sensitivity of HGV detection with two sets of primers, and this technique is applicable for routine screening in clinical laboratories.[53]

A manufacturer (Abbott Laboratories, Abbott Park, IL) has developed a single-tube assay based on RT-PCR amplifying 5′ UTR and followed by oligomer hybridization. All

reagents are contained in a single reaction vial, and detection employs a microparticle enzyme immunoassay in the automated LCx system (Abbott Laboratories, North Chicago, IL).[7]

Recently, Brown and Young reported that, in their experience, some of the primers and probes used to detect HGV also give positive results in samples containing DNA of *Escherichia coli*.[54]

Apart from detection of HGV RNA based on RT-PCR, branched DNA (bDNA) signal amplification pathway assays have been developed; although convenient, they are not as sensitive as RT-PCR assays.[5]

Detection of Anti-Hepatitis G Virus Antibodies

Immunoreactive regions have been identified in the putative nonstructural proteins, particularly NS3, NS4, and NS5, from all three GB viruses, as well as in the putative core protein of GBV.[55,56] In the case of HGV, most immunodiagnostic kits use antigens derived from structural genes of the virus, as for example, recombinant envelope protein E2 expressed in the eucaryotic cell system.[7,57] Antibodies to HGV E2 appeared to be directed toward conformational epitopes, since reactivity in ELISA was not detected with denatured E2 protein.[58] In a study by Feucht et al, the antibodies most frequently found in a group of 709 subjects were antibodies against NS3-NS4 recombinant protein, followed by the NS3 protein and core protein.[56]

PHYLOGENETIC ANALYSIS

The evolutionary relation between the GB viruses and other members of the *Flaviviridae* has been assessed by comparison of nonstructural genes coding RNA helicases and RNA-dependent RNA polymerases.

Within the GB virus family, GBV-A and HGV are more closely related (48% amino acid sequence identity), but they appear unique, with respect to other members of the *Flaviviridae*, in that they do not encode a basic core protein, as do GBV-B and HCV.[7] However, GBV-B bears no more resemblance to HCV than it does to the other GB viruses. It seems that, on the phylogenic tree, the HCV genotypes are tightly grouped on a major branch, GBV-B stands alone on a second major branch, whereas HGV and GBV-A are present on a third major branch, though these viruses further diverge from a common ancestor.[17] Sequence comparison of HGV isolates from different geographic areas indicates that Chinese and Japanese HGV strains may have a closely related ancestry that probably is different from that of American and African strains.[34]

Recently Viazov et al tested 39 blood samples HGV-RNA positive from different parts of the world and reported that on a phylogenic tree all HGV sequences of isolates from Africa, south and southeast Asia were clustered together and were separated from those collected in Europe, North America, and central Asia.[59]

ROUTES OF HEPATITIS G VIRUS TRANSMISSION

Hepatitis G virus is transmitted mainly through blood and blood products.[60-62] In some studies, the median level of serum HGV viremia was found to be about 10 times higher than that of HCV in chronically infected subjects; therefore, the risk of transmission through blood products, sexual contact, or from mother to infant might be higher for HGV than for HCV.[63] The positivity of HGV RNA is about twice as frequent in patients with non-A-E hepatitis following blood transfusion than in sporadic non-A-E hepatitis cases.[4] The high frequency of infection is present in all groups of patients repeatedly exposed to blood products.[4] Among bone marrow transplant recipients who had received transfusions of intravenous immunoglobulin and cellular components, the proportion of HGV-infected subjects was higher than among patients with common variable immune deficiency who had received only intravenous immunoglobulin.[64] In consequence this mode of HGV transmission also occurs during transplantation,[65,66] and with the use of blood-contaminated instruments in intravenous drug addiction. In patients on maintenance hemodialysis, new HGV infections occur without blood transfusions; therefore, HGV may be a marker of nosocomial viral transmission.[67] Sequences of HGV in commercial blood donors or in hemodialysis patients are similar, suggesting spread among restricted groups and nosocomial infection.[34,68] Among professional blood donors, plasmapheresis was identified as a significant risk factor of HGV infection.[69]

Reports indicated that infectiousness of HGV through blood products was low or the clearance of the virus was rapid.[70] Hepatitis G virus RNA was detected in 7 to 40% of commercial plasma pools used for the production of blood products.[71] A high frequency of HGV-RNA contamination (about 100%) in batches of immunoglobulins manufactured without specific viral inactivation procedures has been reported.[72,73] Garcia-Trevijano et al found HGV RNA in 14% of 14 different commercial coagulation-factor concentrates.[74] Despite the prevalence, none,[73,75] or only 12.5 to 14% of recipients of such products were positive for HGV at the time of testing during follow-up.[70,72] In immunocompromised patients, the rate of HGV persistence following blood-borne infection may be higher. One study reported that 7 of 17 (41%) initially HGV-RNA-negative patients who underwent liver transplantation had persistent HGV viremia during follow-up of between 5 months and 4 years.[76]

The possibility of sexual HGV transmission is highly probable but not clear at the moment.[77,78] Persico et al detected HGV RNA in 25 to 50% of samples of seminal plasma obtained from serum HGV-RNA-positive patients.[79,80] The prevalence of HGV RNA was significantly higher in heterosexual partners of HGV-RNA-positive subjects than in those who were HGV-RNA negative.[81] The frequency of infection also was higher in

the group of prostitutes and homosexual men compared with the partners of HGV-RNA-negative subjects.[81,82] There is a high prevalence of HGV infection among non-intravenous drug-using homosexual and bisexual men.[83]

Mother-to-child transmissions of HGV have been shown in several cases.[61,84,85] Among 12 babies born to HGV-RNA-positive mothers, 3 (25%) were HGV-RNA positive at birth.[86] Feucht showed vertical HGV transmission to three of nine (33.3%) babies born to HGV-positive mothers.[87] The rate of HGV mother-to-infant transmission is higher compared with human immunodeficiency virus type 1 (HIV-1) or HCV. The mode of delivery (e.g., elective caesarean delivery) may influence the transmission of HGV.[88] Moaven et al described the case of a breastfed baby born to an HGV-RNA-positive mother. The baby was HGV-RNA negative at birth, but tested HGV-RNA positive at both 4 and 6 weeks of age, without any signs of liver disease.[48]

Hepatitis G virus RNA was detected in saliva of 33% (2/6) of infected subjects.[89] Thus, it is possible that HGV, like other flaviviruses, can be spread horizontally or be transmitted by mosquitoes.[90,91]

PREVALENCE OF HEPATITIS G VIRUS INFECTION

The reported prevalence of HGV infection in selected groups of subjects in some published studies is listed in Table 2. Only some groups of patients were selected for presentation. The frequency of positivity for HGV RNA or anti-HGV antibodies varies among groups, and depending on the subjects' origins and the method used for HGV infection marker detection. Generally, infection with HGV is significantly associated with a history of intravenous drug use, with exposure to transfusions of blood products or dialysis, and with HCV infection, especially with HCV genotype 3a.[63]

Table 2. Reported Prevalence of HGV Infection in Selected Groups of Subjects in Some Published Studies

Number of Cases in Selected Group	Prevalence of HGV Infection Markers: HGV RNA (%)	HGV Ab (%)	Reference Number
Blood donors, mainly voluntary healthy adults			
1478	1.6		16
1048	1.3		61
500	4.2		64
500	1.4		99
448	0.9		68
358	1.1		144
257	1.9		161
257	Not reported	15.9	56
205	1.0		34
200	3.0		162
200	0.5		163
186	1.1	5.4	164
165	1.2		142
150	0.7		69
145	1.4		165
129	0.8		166
125	3.2		72
121	6.6		41
120	4.2		167
100	1.0		38
100	1.0		116
90	2.2		83
81	7.4		168
80	2.5	9.0	97
69	4.3		169
60	1.7	3.3	57
59	3.4		170
50	2.0		171
30	Not reported	3.3	172
Acute non-A-E hepatitis patients			
54	7.4		165
48	2.1		166
45	8.9		96
38	13.2		16
37	10.8		173
31	35.5		38
28	3.6		118
Fulminant non-A-E hepatitis patients			
25	12.0		106
16	37.5		105
16	12.5		174
13	0.0		116
11	0.0		123
10	50.0		103
9	0.0		107
7	42.9		173
7	0.0		175
6	50.0		47
Chronic non-A-E hepatitis patients			
158	9.5		16
76	5.3		142
67	14.9		110
34	5.9		166
20	10.0		116
18	38.9		38
14	64.3	14.3	57
Post-transfusion non-A-E hepatitis patients			
15	26.7		101
13	23.1		16
13 (non-A-C)	23.1		99
8	12.5		98
Non-A-E hepatitis patients			
154	1.9		161
149	8.7		173
126	1.6		52
76	13.2		17
49	36.7		38
12	Not reported	25.0	173
HBV-infected patients			
220	3.2		116
102	6.9		166
100	32.0		96
83	3.6		108
72	9.7		16
58	10.3		66
38	5.3		52
33	21.2		176
23	4.3		163
19	5.3		110

Table 2. continued

Number of Cases in Selected Group	Prevalence of HGV Infection Markers: HGV RNA (%)	HGV Ab (%)	Reference Number
HCV-infected patients			
361	7.4		177
228	21.1		63
207	8.2		52
189	11.1		114
188	8.0		108
179	12.3		166
159	25.3		178
143	5.6		154
128	7.0		179
126	5.6		163
119	24.4		161
117	23.9		113
116	19.8		96
115	15.6		115
107	17.8		16
105	16.2		112
100	19.0		180
100	10.0		116
91	16.6		110
83	26.5		181
74	16.2		152
74	8.1		66
70	25.7		182
63	9.5		99
62	16.1		183
62	16.1		50
53	20.7		122
51	25.5	37.3	56
40	27.5		184
39	20.5		125
34	17.6		89
30	23.3		77
25	8.0		176
22	40.9		118
Autoimmune hepatitis patients			
60	0.0		185
53	9.4		16
Cryptogenic cirrhosis patients			
45	22.2		186
10	0.0		166
Hepatocellular carcinoma patients			
213	5.6		187
139	12.2		165
60	6.0		166
50	16.0		188
39	2.6		189
36	11.1		108
30	6.7		16
30	10.0		116
29	6.9		163
20	40.0		171
16	18.7		117
Hemophiliacs			
95	13.7		72
81	9.9		119
63	23.8		190
49	18.4		16
45	20.0	48.9	172
45	37.8		35
37	2.7		191
17	35.2	52.9	161
10	30.0		116
Hepatitis-associated aplastic anemia patients who did not receive transfusion			
4	50.0		133

Table 2. continued

Number of Cases in Selected Group	Prevalence of HGV Infection Markers: HGV RNA (%)	HGV Ab (%)	Reference Number
Idiopathic aplastic anemia patients who did not receive transfusion			
19	21.0		133
Aplastic anemia patients HAV-HCV negative			
10	30.0		131
B-cell non-Hodgkin lymphoma patients (untreated)			
150	6.0		142
51	2.0		140
Patients on hemodialysis			
519	3.5		68
172	6.4		192
119	16.0		67
100	19.0		193
96	26.0		162
79	54.4		34
78	34.6		170
69	10.1		166
65	15.4		194
61	57.5		195
59	6.8		161
59	Not reported	25.4	56
58	55.2		189
20	15.0		196
Prostitutes			
193	13.9		81
145	11.0		78
140	21.4		82
Homosexual men			
149	13.4		81
Intravenous drug users			
246	15.4		197
130	33.1		53
130	33.1		83
117	35.0		198
99	38.3	41.4	97
95	15.8		173
90	28.9		79
85	75.3		171
70	25.7		182
60	33.3		16
59	28.8		161
59	Not reported	47.5	56
57	31.6		63
52	13.5	40.4	172
49	24.5		179
43	48.8		199
40	32.5	72.5	57
27	3.7	85.2	164
13	15.4		17
40	15.0		116
HIV-infected patients			
100	9.0		71
55	18.2		161
55	Not reported	29.1	56
Cadaver organ donors			
158	17.1		65
Organ or bone marrow transplant recipients			
243 (heart)	23.9		151
221 (kidney)	14.0	39.8	200
109 (liver)	44.9		123
94 (kidney)	42.6		169
89 (marrow)	24.7		64
87 (kidney)	27.5		201
59 (marrow)	42.3		202
44 (liver)	63.6		124
39 (liver)	43.6		111
33 (marrow)	60.6		203

Table 2. continued

Number of Cases in Selected Group	Prevalence of HGV Infection Markers		Reference Number
	HGV RNA (%)	HGV Ab (%)	
25 (liver)	64.0		188
11 (kidney)	54.5		150
11 (kidney)	36.4		192

Only some groups of patients were selected for presentation. Positivity of HGV RNA determined by RT-PCR. Positivity of anti-HGV-protein antibodies (HGV Ab) determined by ELISA.

HEPATITIS G VIRUS AS A HEPATITIS ETIOLOGIC AGENT

The significance of HGV infection as a cause of various hepatitis forms is controversial to date, and it is not known if HGV is a true "hepatitis" virus.[92-94] Patients with aminotransferase elevation of unknown etiology have a low prevalence (13%) of HGV infection and liver histology that is indistinguishable from that of patients without HGV infection.[95] The reported prevalence of HGV infection in cases of acute sporadic hepatitis varies in published studies (see Table 2), but it is low, and HGV seems not to be a serious etiologic agent of acute non-A-E hepatitis.[94] In the course of acute HGV infection, if there is any elevation of aminotransferase levels, it almost always is moderate; therefore, the infection often is undetectable by both patients and physicians. In a study of well-defined community-acquired disease, only 4 of 45 non-A-E hepatitis patients were HGV positive and three of these patients had jaundice, in contrast to the majority of cases of HGV infection.[96] Contrary to the data, 35% of Italian non-A-E acute hepatitis subjects were positive for the HGV genome.[38] In some cases, HGV appearance or clearance (detected with PCR) was accompanied, respectively, by the elevation or sharp decrease in serum transaminase concentration.[62,97]

Hepatitis G virus RNA is detectable in about 20% of post-transfusion non-A-E hepatitis cases (see Table 2). The disease often is mild, and elevated serum transaminase concentrations are found in only a small percentage of cases.[98-101] In acute post-transfusion hepatitis with HGV infection alone, serum alanine transaminases were elevated for 2 to 8 weeks and resolved 5 months after transfusion.[100,101] The course of infection was studied in some cases, and was accompanied by virus clearance in the majority of immunocompetent patients.[99,100] In some patients, however, both HGV RNA and elevated aminotransferase levels persisted over a longer period.[99,102] The clinical pictures of acute infection with HCV alone or HCV-HGV co-infection are similar.[100]

In some countries, HGV infection often is found in patients with fulminant non-A-E hepatitis (see Table 2). The significance of this is controversial, as almost no cases of fulminant hepatitis were induced by transfusion of blood products negative for HBV or HCV infection markers.[94] However, it could not be excluded that a small, but significant percentage of fulminant hepatitis cases may be attributable to HGV infection, especially in association with other hepatitis viruses,[103] but also alone.[103-106] In addition, Heringlake et al reported a specific strain of HGV associated with non-A-E fulminant hepatitis in German patients,[103] and Yoshiba et al showed that therapeutic transfusion-mediated transmission of HGV after the onset of fulminant hepatitis had only a minor role in overall HGV-RNA positivity.[105] However, it also was shown that HGV is not usually present in cases with fulminant hepatitis on initial diagnosis.[107] As proposed by Sugai et al, most HGV strains may induce mild or subclinical liver disease, although some HGV variants might have high disease-inducing activity, caused, for example, by active replication mutations.[108]

A high percentage of HGV-RNA-positive non-A-E hepatitis in Italian patients was reported.[38] The authors assumed that the prevalence should be similar to that in other published studies, but the detection method strongly influenced results. In addition, they wrote that it could not be excluded that apparently HGV-negative patients had actually been infected with HGV variants that escaped detection.

In the majority of published studies, HGV infection has not been associated with serious chronic liver disease.[94] In a minor number of clinical studies, the association between HGV infection and greater activity of liver enzymes was reported, but only some of the subjects tested had levels considerably higher than normal.[13,109] Colombatto et al reported the association between elevation of cholestatic enzymes and nonspecific inflammatory bile duct lesions with HGV infection.[110] They assumed that a lesion of the bile duct leading to such elevation might be specific for HGV, and suggested that HGV detection should be a routine diagnostic element of cholestatic syndromes of unknown etiology.[111] In many observations, there was no correlation between HGV infection and elevation of cholestatic enzymes. Although co-infection with HGV does not influence the clinical course or histopathologic picture of chronic HBV or HCV infection in most cases,[63,98,112-117] in some, HGV seems to interfere with HCV and helps eliminate it: the HCV viremia in HGV co-infected patients was about twofold lower than in patients with HCV infection alone.[99,118,119] Hepatitis G virus is not likely to be the cause of the majority of cases of cryptogenic cirrhosis,[120] but in about 10% of such cases HGV infection was the only identifiable cause of chronic disease.[121] Japanese leprous patients infected with HGV alone did not have elevated serum aminotransferase levels.[46] Sugai et al detected HGV more frequently in patients with liver cirrhosis than in those with chronic hepatitis, and they suspected the possible role of HGV in aggravating liver disease.[108]

During liver transplantation, pretransplant HGV viremia has been reported to be associated with post-transplant viremia in 50 to 80 or 100% of cases.[111,122,123] In the absence of HBV or HCV infection in liver transplant recipients, the prevalence of HGV infection has no influence on the graft.[111] Co-infection with HGV-HBV or HGV-HCV does not increase the frequency of occurrence of post-transplant graft hepatitis and overall clinical profile of patients.[66,111,124,125] Moreover, a significant tendency toward a lower number of cases of graft hepatitis in HGV-HCV co-infected patients compared with patients with HCV infection alone has been reported.[66] However, Murthy et al observed a higher risk of post-transplantation liver disease among the recipients of renal transplant with pretransplantation HGV infection.[126]

The prevalence of HGV RNA in patients with autoimmune hepatitis does not differ significantly from that in blood donors.[127] One case has been described of long-term liver dysfunction with liver enzyme elevation after bone marrow transplantation in which HGV was the only known hepatitis virus isolated.[102]

In two series, babies who were HGV-RNA positive at birth or later, showed no signs of liver disease over a follow-up of about 1 year.[86,87]

Results obtained by Kudo et al probably explain the small contribution of HGV infection to the severity and progression of liver disease in HCV-co-infected subjects.[128] In liver samples, the estimated amount of HCV RNA was about 10,000 times more than HGV RNA; nevertheless, the serum amounts were similar.[128] Therefore, the rates of viral replication in liver tissue must differ strongly, and in addition, HGV seems to replicate in other tissues. Laskus et al similarly reported absence of detectable HGV replication in liver tissue samples obtained from both HGV- and HCV-infected patients with similar serum levels of the RNA of the viruses.[129]

HEPATITIS G VIRUS INFECTION AND OTHER DISEASES

The possible role of HGV infection in the pathogenesis of some rare non-liver diseases has been suggested, but it is too early to say that HGV is an etiologic agent of these. However, currently, the role of HGV cannot be excluded.

Aplastic anemia is sometimes preceded by hepatitis, frequently of unknown origin. Hepatitis A, B, and C viruses have been excluded as the responsible agents.[130,131] In some cases of hepatitis-associated aplastic anemia, HGV was the only infectious agent detected, even if the patients had not received any transfusion before diagnosis.[130-134] Moriyama et al detected HGV RNA in only 5 of 18 patients with aplastic anemia who had received blood transfusions before testing, but in none of eight patients who had not received transfusions.[135] The data were consistent with those reported by Brown et al, who found HGV RNA in 26.3% of patients with aplastic anemia and in 23.1% of multiply transfused control patients (difference not statistically significant).[136] In contrast to these data, Kiem et al detected HGV RNA in 26.1% of 23 serum samples obtained from both subjects with hepatitis-associated aplastic anemia and those with idiopathic aplastic anemia who did not receive transfusions.[134] They concluded that although transfusions are a major source of HGV infection in serum of patients with aplastic anemia, the increased prevalence of HGV RNA in subjects not transfused suggests involvement of HGV in the development of aplastic anemia, whether associated with hepatitis or not.[134]

In some studies the prevalence of HGV infection was significantly higher in patients with hepatocellular carcinoma (HCC) compared with the healthy population or patients with chronic hepatitis.[108,116,137,138] Therefore, HGV could be a risk factor for HCC.[137] Berg et al reported a significantly higher prevalence of HCC in patients with HGV and HCV co-infection compared with patients with HCV infection alone,[66] and they speculated that HGV co-infection in chronic HCV-infected patients may be a cofactor in the development of HCC.

The HGV, like HCV, infection was suspected to be one of the factors initiating non-Hodgkin lymphomas or mixed cryoglobulinemia. In contrast to HCV infection, however, data on prevalence of HGV infection in lymphoma or cryoglobulinemia patients do not support the hypothesis that this virus also may play a major role in lymphomagenesis. or in the production of mixed cryoglobulinemia.[139-141] Nevertheless, HGV prevalence in Italian patients with B-cell non-Hodgkin lymphoma was significantly higher than in healthy subjects,[142] and HGV infection should be studied to clarify all other clinical implications of this infection.

The data presented, taken together, show that HGV is not a classic hepatitis virus, and it may cause liver damage in only a small percentage of infected persons. These results are consistent with rare findings that HGV may be primarily a lymphotropic agent, like Epstein-Barr virus, and may cause hepatitis only under special circumstances.[13,143] Hepatitis G virus RNA also may be detected in peripheral mononuclear blood cells (PBMC) of serum in HGV-negative patients.[144] However, in *Flaviviridae*, the presence of antigenomic (minus) RNA strand is considered to be evidence of viral replication. Madejon et al found the genomic strands of HGV RNA in serum, liver, and peripheral blood cell samples obtained from patients with chronic hepatitis B, C, or D, but antigenomic strands were found only in liver samples.[145] Saito et al detected plus-stranded HGV RNA in serum and liver samples obtained from six patients with hepatitis and in PBMC samples from five of the patients, but minus-stranded in only six liver, two serum, and one PBMC sample.[146] Generally, the HGV-RNA-negative strand is only rarely detected

in PBMC; it has not been established whether HGV actively replicates there,[147] nor is it known whether it replicates in lymph nodes. The replication of HGV is also possible in human cultured-cell lines, both those derived from a human T-cell leukemia virus infected T-cell line and a non-neoplastic human hepatocyte line.[148]

HUMAN IMMUNE SYSTEM AND HEPATITIS G VIRUS INFECTION

Anti-E2 antibodies to HGV can be detected by commercially available tests. E2 is an HGV surface protein, and this antigen has been presumed to be a target for host humoral immune response.[55,56,97] The seroconversion to anti-E2 antibodies is often associated with loss of detectable HGV viremia,[97] and detection of anti-E2 antibodies may be useful for diagnosing recovery from HGV infection. However, it is not known how many years anti-E2 positivity remains. In addition, some patients became HGV-RNA negative without developing an anti-E2 immunity.[97] Nevertheless, the E2 antibodies seem to be a tool of effective response. Similarly, only the minority of subjects with either HGV-RNA or anti-HGV recombinant protein (NS3-NS4, NS3, or core) antibody positivity showed HGV nucleic acids and antibody response in parallel.[56] Because of the lack of hypervariable regions in HGV genome, the virus would use a strategy for persistence other than immune escape.[31]

In a number of studies, a higher occurrence of chronic HGV infection was reported in immunosuppressed patients compared with immunocompetent subjects,[64,149,150] but, for example, Wolff et al did not find any relation between immunosuppression and HGV infection.[151]

Once acquired, HGV infection may persist for many years in infected subjects, but not all the possibilities of HGV resistance currently are known.

HEPATITIS G VIRUS AND ANTIVIRAL AGENTS

There are conflicting opinions concerning the sensitivity of HGV to antiviral therapy: in some studies it seemed to be similar to HCV,[114,115] but independent[152]; however, the response may be different.[153,154]

During interferon-α (IFN-α) therapy, the serum HGV-RNA level decreases in most patients treated, and it may become undetectable.[63,114,115,152,154,155] Peripheral mononuclear blood cell HGV RNA was preferentially sensitive to interferon treatment and usually became undetectable shortly after the initiation of the treatment, despite the possibility of sustained presence of HGV RNA in serum or plasma.[144] In only a small percentage of these patients the response was sustained and after the discontinuation of treatment HGV viremia returned in most or all subjects.[13,63,114,115,154,156,157] The sustained response was more probable in patients with a low pretreatment virus load.[152,154]

In the cases of HGV-HCV co-infection Tong et al found that HGV infection was more common in patients with chronic HCV infection that did not respond to IFN-α compared with those who did,[157] but this was an isolated finding. Contrary to their opinion, most researches detect no influence of HGV infection in response to IFN-α in patients with chronic hepatitis C.[63,114,154]

Ribavirin has no potent anti-viral activity against HGV.[158,159]

CONCLUSIONS

The sensitivity of the HGV-detection methods still has not been established in detail. Recent results have shown that the virus is globally distributed, parenterally transmissible, and can induce persistent viremia in humans. In the majority of reported studies, HGV seems to be an "accidental tourist,"[94,160] but some findings suggest that, in some cases, it may be a serious pathogenic agent. Further studies are necessary to obtain sufficient data on the role of HGV in human pathology.

NOTE

Since this article was accepted for publication, numerous additional studies on HGV have been reported, but the general opinion of its low or only conditional pathogenicity and worldwide prevalence has not changed.[204,205] A new pathogen, namely, transfusion-transmitted virus (TTV) has become a new focus of viral hepatitis research. This is a DNA nonenveloped virus with numerous similarities to HGV: worldwide distribution,[206,207] low disease causative capability,[208,209] interferon sensitivity,[210] significant sequence heterogeneity both in infected persons and in different geographic regions[211,212] and presence in blood and other tissues, including stool.[213]

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