MAJOR ARTICLE

Cytomegalovirus gN Genotypes Distribution among Congenitally Infected Newborns and Their Relationship with Symptoms at Birth and Sequelae

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Background. Cytomegalovirus (CMV) is the leading cause of congenital infection, with morbidity and mortality at birth and sequelae. Both host and viral factors may affect the outcome of infection. CMV strain virulence may depend on genetic variability in "key genes," such as UL73, which encodes the envelope glycoprotein gN. This study aimed to ascertain the role of gN variants as markers of pathogenicity and prognosis in newborns congenitally infected with CMV.

Methods. Seventy-four congenitally infected newborns were monitored for symptoms of CMV disease at birth and during long-term follow-up. The distribution of gN variants was analyzed in relation to virological parameters, clinical signs, laboratory and instrumental abnormalities at birth, and sequelae. Multivariate cluster analysis was used to test for differences in the distribution of variables. An independent validation cohort of the same size and modality of recruitment as the original population was examined by logistic regression to validate results.

Results. Univariate and cluster analyses suggest that newborns congenitally infected with CMV fall into 2 subpopulations on the basis of definite parameters of CMV disease. The first population with no symptoms at birth, negative instrumental findings, and a favorable long-term outcome was significantly associated with gN-1 and gN-3a genotypes. The second group with symptoms at birth, abnormal imaging results, and sequelae was associated with gN-4 genotypes ($P < .05$). The validation cohort further supports the results, indicating that genotypes gN-1 or gN-3a reduce the risk of sequelae 5 fold (95% confidence interval, 1.3–15.6 fold), whereas variants belonging to group gN-4 increase the risk of sequelae 8 fold (95% confidence interval, 2.6–25.8 fold).

Conclusions. Results suggest that gN genotypes might be markers for virulence of CMV wild-type strains and a discriminating factor for selection of CMV-infected newborns who are at risk of developing sequelae.

Cytomegalovirus (CMV) is the most common congenital infection, and its prevalence ranges between 0.2%–2.2% in newborns [1, 2]. Ten percent of congenitally infected newborns are symptomatic at birth (mortality rate, 20%–30%), and permanent neurological injury occurs in up to 60% of these infants [3, 4]. In addition, 5%–15% of asymptomatic newborns may develop sequelae, namely psychomotor impairment and sensorineural hearing loss [2–5]. Both host and viral factors may affect the outcome of congenital CMV infection [6].

Assessment of neurodevelopmental outcome is currently associated with cerebral involvement, disclosed by peculiar symptoms at birth, neuroimaging [7–9], and conditioning treatment [10]. Therefore, the availability of other reliable markers for the identification of newborns at higher risk of developing symptomatic infection and/or sequelae may be crucial to provide a prognosis for targeted management of infected infants.

CMV strains may vary in virulence, tropism, and "pathogenic potential," which is probably related to genetic variability exhibited among wild-type isolates by "key genes" for viral biology [11–14]. CMV open reading frame (ORF) UL73 is a highly polymorphic gene among clinical strains [14]. It encodes the envelope glycoprotein N (gN), a gC-II component impli-

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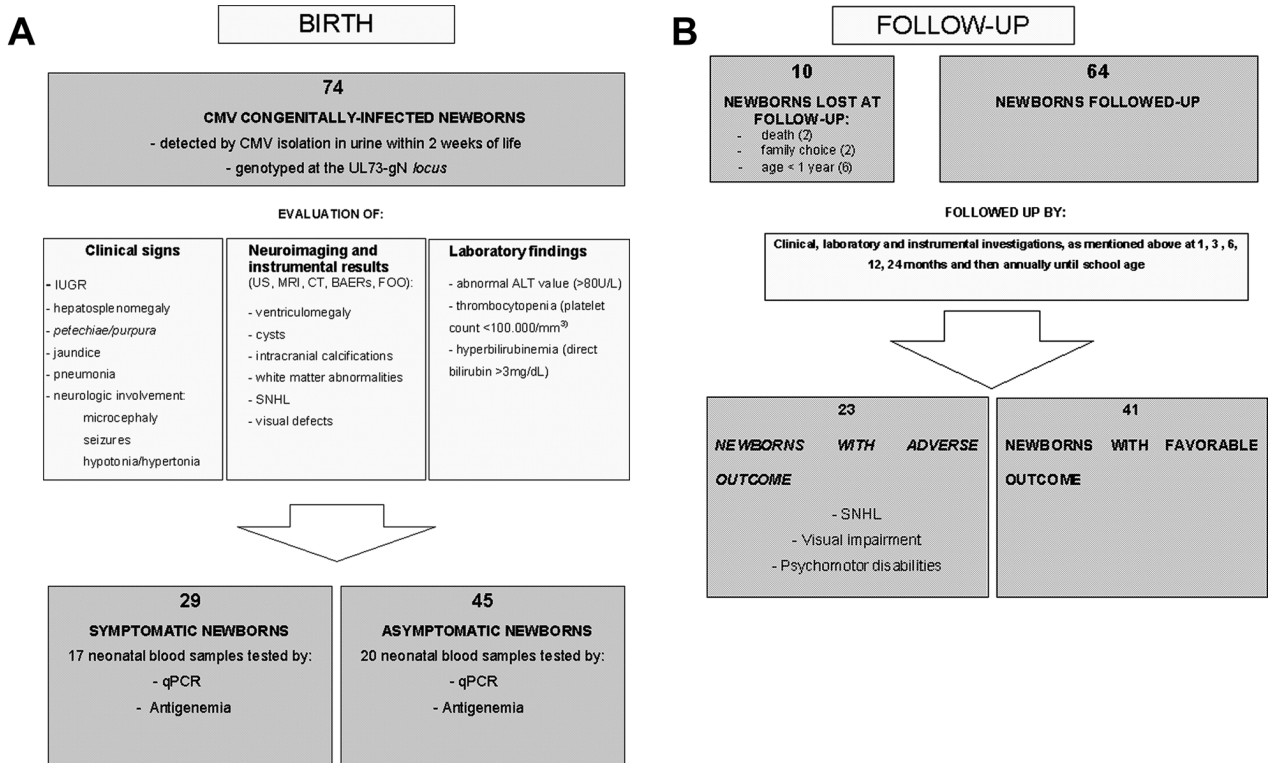

Figure 1. Population examined in the present study and genotyped for gN. BAERs, brainstem auditory evoked responses; CT, computed tomography; FOO, fundus oculi; IUGR, intrauterine growth retardation; MRI, magnetic resonance imaging; SNHL, sensorineural hearing loss; US, ultrasound.

cated in virus attachment to the host cell and spread [15, 16]. The UL73 locus has a polymorphic region with 8 identified gN genomic variants (gN-1, gN-2, gN-3a, gN-3b, gN-4a, gN-4b, gN-4c, and gN-4d) [17–19]. This work analyzed the distribution of gN genotypes in a cohort of symptomatic and asymptomatic congenitally CMV-infected newborns and attempted to ascertain the link between gN variants and clinical and neurological findings at birth and long-term sequelae.

METHODS

Patients and clinical examinations. The study population included 74 congenitally infected newborns enrolled from January 1998 through May 2008 and monitored under a surveillance program for CMV congenital infection by the Neonatal Intensive Care Unit Microbiology and Obstetrics and Gynecology Divisions of the University of Bologna, Italy. Informed consent was obtained from the parents of infants.

Newborns from pregnant women with confirmed acute CMV infection or displaying clinical signs of CMV infection at birth and confirmed congenitally infected by virus isolation from their urine within the first 2 weeks of life were considered to be eligible. The newborns with diseases that might have been potential confounders (eg, human immunodeficiency virus–CMV coinfection) were excluded. The time of CMV infection was dated and determined as primary, in mothers with established seroconversion, or recurrent.

All infants were investigated for the presence of symptoms at birth, and 64 of them monitored during a long-term follow-up by clinical, instrumental, and laboratory evaluations, as described elsewhere [20] and summarized in Figure 1. Briefly, infected newborns were classified as having symptomatic or asymptomatic infection on the basis of $\geqslant 1$ of the following findings: (1) clinical signs (intrauterine growth retardation, hepatosplenomegaly, petechiae/purpura, jaundice, pneumonia, or neurologic involvement); (2) neuroimaging findings by ultrasound and/or magnetic resonance imaging, and/or computed tomography (cerebral calcifications, germinal matrix cysts, ventriculomegaly, and cerebellar hypoplasia); (3) sensorineural defects (hypoacusia, visual impairment); and (4) laboratory findings (abnormal transaminase value, thrombocytopenia, and hyperbilirubinemia).

Sixty-four infants were followed up from birth at 1, 3, 6, 12, and 24 months of life, and annually thereafter. Clinical examinations included measurement of anthropometric parameters and assessment of the relative percentile. Clinical tests included the following: (1) cranial ultrasound of all case patients within the first 2 weeks of life and repeated at 1 and 3 months of age; neonates with abnormal ultrasound findings

were re-examined weekly by ultrasound during the first month of life and then monthly, confirmed by cranial computed tomography and/or magnetic resonance imaging; (2) ophthalmologic examination was undertaken in the neonatal period and at 6 and 12 months of life; (3) hearing function was assessed by brainstem auditory evoked responses in the first 3 months of life, at 6 and 12 months of age, and yearly by behavioral audiometry until school age; and (4) psychomotor development was assessed at 6, 12, and 24 months of age with use of the Brunet-Lezine test.

All investigations classified the newborns as asymptomatic or symptomatic at birth with a favorable or adverse long-term outcome. Healthy infants were described as having a favorable outcome, whereas infants displaying sequelae derived from CMV congenital infection were described as having an adverse outcome.

The 2 main independent investigators (S.P. and M.L.) who performed genotyping and clinical data assembly/collection, respectively, were blinded to reciprocal findings. An independent cohort was also selected to validate results obtained from the study group. This validation cohort consisted of 67 congenitally CMV-infected newborns, and follow-up data were available for 64.

DNA extraction, polymerase chain reaction (PCR) amplification, and genotyping of UL73. DNA extraction was performed directly on urine samples of newborns with use of QIABlood kit with BioSprint15 (Qiagen), according to the manufacturer's instructions. ORF UL73 was PCR-amplified with use of a nested PCR method described elsewhere [21]. Automated DNA sequencing (Primm) was performed to assign each CMV isolate tested to 1 of the 8 gN genotypes, as described elsewhere [19]. Sequencing and phylogenetic analyses were performed using the MegAlign program package (Lasergene, version 7.0; DNAStar).

Virological parameters. Virus isolation from urine and antigenemia assay were performed as described elsewhere [22, 23]. Results of antigenemia assays were expressed as the number of pp65-positive cells per 1×10^5 polymorphonuclear leukocytes. Quantitative assessment of viral DNA load in neonatal blood was performed using the COBAS AMPLICOR CMV MONITOR test (Roche Diagnostics), according to the manufacturer's instructions; results were reported as the number of DNA copies per 1×10^5 polymorphonuclear leukocytes [20].

Statistical analysis. Data were analyzed using the SPSS software package, version 13 (SPSS). Continuous variables are described as means or medians and categorical data as percentages. Two-step cluster analysis was used to divide cases into uniform groups on the basis of either categorical or continuous data. The choice of a similarity measure and the determination of the number of clusters were based on the log-likelihood distance and Schwarz's Bayesian Criterion, respectively. χ^2 test with Bonferroni correction was used to test the statistical significance.

A validation data set of 64 subjects was generated to verify independently whether the genotype was significantly associated with the outcomes (symptoms, sequelae, and neuroimaging abnormalities). Logistic regression analysis was performed on the validation data set to assess the multivariate association between the prognostic factors identified by cluster analysis on the study population.

All reported P values are 2-sided. P values $<.05$ were considered to be statistically significant.

RESULTS

Study population and genotypic frequencies of gN variants. Seventy-four live newborns (44 male and 30 female sex) with CMV infection acquired in utero were enrolled in this study. Full neonatal anthropometric parameters were available for 59. Although 13 (22%) of 59 were preterm infants (>30 or <37 completed weeks of gestation), the majority (45 [76.3%] of 59) were born at term.

The general distribution of the detected gN variants among CMV isolates from the 74 newborns was as follows: gN-1, 15 cases (20.3%); gN-2, 6 cases (8.1%); gN-3a, 6 cases (8.1%); gN-3b, 5 cases (6.8%); gN-4a, 15 cases (20.3%); gN-4b, 10 cases (13.5%); gN-4c, 17 cases (22.9%); and eighth gN genotype, 0 cases [17, 19]. See the Appendix, which appears only in the online version of the journal, for additional details.

As summarized in Figure 1, the population examined consisted of 29 (39.2%) symptomatic and 45 (60.8%) asymptomatic infants at birth; 2 (2.7%) died during the first weeks of life. Follow-up data were available for 64 children (86.5%).

CMV gN genotypes versus neonatal parameters. The neonatal parameters divided according to the gN variant exhibited by CMV strains are summarized in Table 1. Only symptoms at birth lacked homogeneity across the different genotypes ($P < .05$).

Cluster analysis performed on genotypes versus pregnancy trimester of mother's seroconversion, gestational age, cranial circumference, and birth weight distinguished 2 groups of newborns (Bayesian Criterion, 498.44; ratio, 1.780). Of the 46 subjects combined (limiting datum, trimester of the mother's seroconversion during pregnancy), 24% fell into the first cluster and 76% into the second. The first group, characterized by genotypes gN-1 and gN-3a, was associated with birth at term and cranial circumference and birth weight superior to the mean of the total population. The second group was characterized by gN-4 genotypes and associated with preterm birth and cranial circumference or birth weight inferior to the mean of the total population. However, only gestational age and birth weight significantly ($P < .05$) contribute to generate the clusters, suggesting both that the time of the mother's seroconversion

Table 1. Neonatal Overview of the 74 Newborns Congenitally Infected with Cytomegalovirus

Genotype	GA,[a] weeks	GA <10th percentile	CC,[a] cm	CC <10th percentile	BW,[a] g	BW <10th percentile	NIA[a]	Symptomatic[b]
gN-1	38.9 (39; 35–40)	2/15 (13.3)	33.9 (34; 30–35.5)	1/15 (6.7)	2989 (3063; 1950–3900)	0/15 (0)	2/15 (13.3)	2/15 (13.3)
gN-2	38.8 (39; 37–40)	1/5 (20)	33.6 (33.5; 32–36)	0/5 (0)	3336 (3130; 2950–4200)	0/5 (0)	1/6 (16.7)	1/6 (16.7)
gN-3a	39 (39; 39–40)	0/5 (0)	33.9 (33.5; 33.4–35)	0/5 (0)	3188 (3260; 2880–3480)	0/5 (0)	0/6 (0)	0/6 (0)
gN-3b	38.8 (40; 38–40)	1/5 (20)	33.5 (33.5; 33–34)	0/5 (0)	2931 (2980; 2335–3430)	0/5 (0)	2/5 (40)	1/5 (20)
gN-4a	37.4 (38; 33–40)	4/12 (33.3)	33.7 (34; 31–36)	1/12 (8.3)	2776 (2980; 1655–3320)	1/13 (7.7)	6/15 (40)	10/15 (66.7)
gN-4b	39.5 (40; 38–40)	0/5 (0)	34.3 (34.3; 33.5–37)	2/7 (28.6)	3277 (3337.5; 2750–3685)	0/5 (0)	6/9 (66.7)	6/10 (60)
gN-4c	36.5 (36.5; 30–40)	5/10 (50)	32.3 (33; 26–37)	1/10 (10)	2788 (3080; 840–3830)	1/10 (10)	4/13 (30.8)	9/17 (52.9)
Total	38.2 (39; 30–40)	13/57 (23)	33.5 (33.5; 26–37)	5/59 (8)	2983.3 (3100; 840–4200)	2/58 (3)	21/69 (30)	29/74 (39)

NOTE. Data are proportion (%) of patients or mean value (median; range). The neonatal features examined (gestational age, anthropometric measures, instrumental, and clinical findings) are divided according to gN genotype. BW, birth weight; CC, cranial circumference; GA, gestational age; NIA, neuroimaging abnormalities.

[a] $P > .05$, for comparison across genotypes.

[b] $P = .006$, for comparison across genotypes.

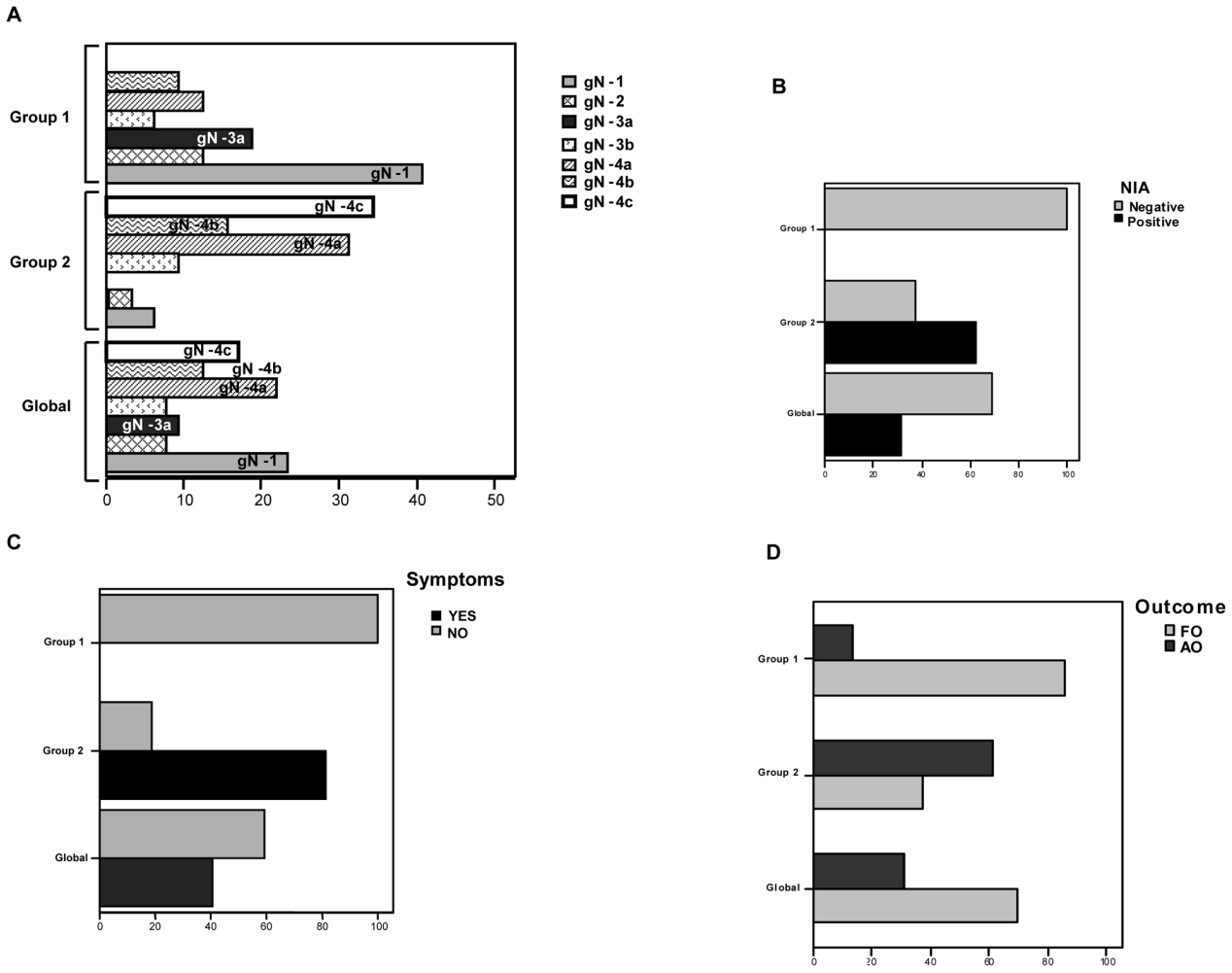

Figure 2. Multivariate cluster analysis of newborns enrolled in this study. The following parameters have been reported: percentage within cluster of genotypes (*A*), percentage within cluster of neuroimaging abnormalities (NIA) (*B*), percentage within cluster of symptomatology at birth (*C*), and percentage within cluster of favorable outcome (FO) or adverse outcome (AO) (*D*). Percentages are reported on the *x* axes.

was not a bias to our data and that gN genotypes do not significantly influence the neonatal parameters considered.

CMV gN genotypes versus symptomatology, virological parameters, and neuroimaging findings at birth. Symptoms at birth were determined by analyzing the presence of ⩾1 of the clinical signs, neuroimaging results, sensorineural defects, and laboratory findings as detailed in Figure 1 and Table 1.

Although gN-1 and gN-3a were found in almost all the examined cases among asymptomatic newborns (gN-1, 13 [86.7%] of 15 were asymptomatic; gN-3a, 6 [100%] of 6 were asymptomatic), the gN-4 variants were preferentially detected among infants with symptomatic infection. In particular, gN-4a, gN-4b, and gN-4c were found among symptomatic newborns in 10 (66.7%) of 15, 6 (60%) of 10, and 9 (52.9%) of 17 cases, respectively.

Virological parameters were also tested in a minority of infants, depending on neonatal blood availability. Quantitative PCR results were available for 51 of 74 newborns, whereas antigenemia was tested in 37 of 74 newborns. Thirteen of these 37 were both pp-65 and qPCR positive. The number of newborns with positive results of the antigenemia assay was higher among those with gN-4a and gN-4b variants (7 of 12 and 3 of 5, respectively), whereas the group of newborns with gN-1 and gN-2 had only 1 pp65-positive case, and gN-3a and gN-3b groups did not show any positivity for the pp-65 CMV antigen.

The viral load in neonatal blood was also analyzed according to the gN-specific strain. Considering a "prognostic-pathological" cut-off of 10^3 genome copies per 100,000 polymorphonuclear leukocytes [20], gN variants distribution did not significantly differ between cases with greater than or less than 103 genome copies per 100,000 polymorphonuclear leukocytes. Most of the abnormal neuroimaging results (16 [76.2%] of 21) obtained by ultrasound and confirmed by computed tomog-

Table 2. Comparison between the Study Population and the Validation Cohort

Genotype	No (%) of patients		Proportion (%) of patients					
			Symptoms at birth		Neuroimaging abnormalities		Adverse outcomes	
	VC[a] (n = 67)	SP[b] (n = 74)	VC	SP	VC	SP	VC	SP
gN-1	11 (16)	15 (20.3)	1/11 (9.09)	2/15 (13.3)	1/11 (9.09)	2/15 (13.3)	1/11 (9.09)	3/12 (23.10)
gN-2	9 (13.43)	6 (8.1)	2/9 (22.22)	1/6 (16.7)	1/9 (11.11)	1/6 (16.7)	2/8 (25)	1/5 (20)
gN-3a	14 (20.9)	6 (8.1)	3/14 (21.43)	0/6 (0)	3/14 (21.43)	0/6 (0)	3/13 (23.08)	0/6 (0)
gN-3b	7 (10.45)	5 (6.8)	2/7 (28.57)	1/5 (20)	0 (0)	2/5 (40)	1/7 (14.29)	2/5 (40)
gN-4	26 (38.81)	42 (56.7)	13/26 (50)	25/42 (60)	10/26 (38.46)	16/37 (43.24)	16/25 (64)	13/30 (43)

NOTE. SP, study population; VC, validation cohort. No significant differences ($P > .05$) between VC and SP were observed for symptoms at birth, neuroimaging abnormalities, or adverse outcomes.

[a] Sixty-four cases were available for cluster analysis.

[b] Sixty-four cases were available for regression analysis.

raphy and/or magnetic resonance imaging (21 of 69) were in newborns with the gN-4 variants.

CMV gN genotypes versus long-term outcome. Sixty-four children included in this study were monitored for clinical, laboratory, and instrumental signs of CMV disease during at least a 1-year follow-up. Follow-up examinations were not available for all newborns because of neonatal deaths (2) or family choice (2), or because enrolled newborns were aged <1 year (6). The mean duration of the follow-up period for the study population was 20.8 months after birth (median, 18 months; range, 6–60 months).

Children were classified into the following 2 groups: those with favorable outcome (41 cases without sequelae derived from CMV congenital infection) and those with adverse outcome (23 cases with sequelae), mainly consisting of psychomotor impairment, visual deficit, and sensorineural hearing loss. The children without sequelae who had favorable outcomes included 76.9% of those with gN-1, 80% of those with gN-2, and 100% of those with gN-3a, whereas the variants belonging to the gN-4 group were associated with adverse outcome in 36.4% of cases for gN-4a, 55.5% for gN-4b, and 50% for gN-4c subgroups, which together represent the majority of infections that resulted in sequelae (68.4%).

Multivariate cluster analyses. Multivariate analysis combined the following parameters: gN genotype, neuroimaging abnormalities, symptomatology at birth (presence or absence), and long-term outcome (favorable or adverse). Results are summarized in Figure 2. The 2-step cluster analysis yielded 2 groups on the basis of the Schwartz's Bayesian Criterion (459.94) and the highest log-likelihood distance measures (ratio, 1.944); 64 subjects were combined and equally shared between clusters. Group 1 was characterized by genotypes 1 and 3a and was associated with newborns without symptoms at birth and/or neuroimaging abnormalities who displayed favorable outcome. Group 2 was marked by gN-4 genotypes, associated with symptomatic newborns, neuroimaging abnormalities, and displaying adverse outcome. The contribution of each of the above factors to both clusters was statistically significant ($P < .05$).

After introducing the antigenemia parameter in the clustering process, 2 clusters were again observed (Bayesian Criterion, 289.96; ratio, 3.406), and 37 subjects were combined (54% in cluster 1 and 46% in cluster 2). Negative antigenemia values were linked to group 1 (genotypes 1–3a, no symptoms, no neuroimaging abnormalities, and no adverse outcome), whereas positive pp65 antigenemia was associated with cluster 2 (genotypes 4, symptoms at birth, neuroimaging abnormalities, and adverse outcome).

Validation data set. An independent validation cohort was selected using the same inclusion criteria, clinical features, and modality of recruitment as in the study population. Sixty-seven congenitally infected newborns were included in the validation cohort, and a long-term follow-up was available for 64 of them (1 died during the neonatal period; 2 were aged <1 year). The validation population was similar to the study group in all baseline characteristics (Table 2), and in particular, no statistically significant difference ($\chi^2 = 7.44$; $P = .11$) was found between the 2 populations with regard to gN genotypic frequencies (gN-1, 11 cases [16.4%]; gN-2, 9 cases [13.4%]; gN-3a, 14 cases [20.9%]; gN-3b, 7 cases [10.5%]; gN-4a, 6 cases [9%]; gN-4b, 6 cases [9%]; and gN-4c, 14 cases [20.9%]). Moreover, no significant differences ($P > .05$) between the validation cohort and the study population were observed with regard to symptoms, neuroimaging abnormalities, or sequelae.

The validation cohort was examined by logistic regression analysis. Results showed that the selected prognostic factor correlates with the sequelae. Genotypes gN-1 or gN-3a are associated with a 5-fold reduction in the risk of sequelae (relative risk, 4.524; 95% confidence interval, 1.3–15.6), whereas variants belonging to group gN-4 are associated with an 8-fold increase in the risk of sequelae (relative risk, 8.127; 95% confidence interval, 2.6–25.8). The disappearance of symptoms and neu-

roimaging abnormalities in the logistic model may be explained by their high well-known association with sequelae ($P < .001$).

DISCUSSION

The availability of reliable markers for the identification of congenitally infected newborns at higher risk of developing symptomatic CMV infection and/or sequelae may have a significant impact on both the eligible monitoring steps during follow-up and an early therapeutic/rehabilitative intervention to minimize long-term damage. Currently, the only scientific evidence to reduce sensorineural hearing loss is drug therapy for patients with cerebral involvement [10]. Furthermore, although it is universally known that some of the larger group of asymptomatic newborns may develop sequelae, prognostic markers and therapeutic indications for these infants are currently lacking.

Here, we suggest the investigation of virological markers as potential prognostic factors to gauge the severity of congenital CMV infection. Other research has sought such a marker in the viral load in neonatal blood and urine, which seems to be related to symptomatic disease at birth [20, 24–26] and appears to be prognostic of adverse outcome [20, 26].

The importance of the infecting CMV strain for clinical outcome has long been a matter of speculation [27]. Genetic and immunologic variability may affect CMV virulence, irrespective of viral load [28].

Studies on this topic in congenitally acquired CMV have mainly been performed on UL55-gB and UL144 genes and have provided conflicting results [6, 14, 29–35]. The failure to use sequence information to predict disease outcome is probably attributable to the use of low variability ORFs (9.5% for gB) or intragenic recombination [12] (both gB and UL144 present chimeras), which may explain why gB and UL144 do not seem to be good markers for phenotypic differences among wild-type CMV strains.

The present work focused on the distribution of gN polymorphisms in a population of infected newborns and attempted to find a link between this crucial glycoprotein and the severity of congenital CMV infection at birth and thereafter. The uniqueness of this study is the large number of cases collected and monitored during follow-up by clinical, laboratory, virological, and instrumental investigations both in the study and validation cohorts. In addition, this work analyzed a highly polymorphic (50% variability) essential viral protein with well-characterized biochemical properties [15, 16, 35].

Other studies [36–38] analyzing the correlation between CMV gN genotypes and clinical outcome have suggested that gN-1 could represent a less virulent virus phenotype, whereas the gN-4 group was predominantly associated with severe manifestations. Our present findings among congenitally infected newborns, supported by detailed clinical data and a blind multivariate approach, confirm what was previously hypothesized for gN-1 [14, 21, 37, 38] but also indicate that gN-3a seems to be the mildest virulence type, together with gN-1; the gN-4 group is still associated with serious illness, as has been demonstrated in transplant patients [37]. The present results were further validated by logistic regression analysis of an independent validation cohort, which suggests that the gN-1 variant lowers the risk of sequelae 5 fold with respect to the other genotypes, whereas variants belonging to gN-4 group increase the risk of sequelae 8 fold. Clinically, sequelae constitute the most reliable parameter suggesting a differential virulence between gN-1 or gN-3a and the gN-4 subgroups.

Recent reports [35] disclosed a 30% strain-specific anti-gN neutralization response during natural infection, which seems to act significantly better against the gN-4 recombinant virus, expressing the gN-4a variant. Although transmission and outcome of intrauterine CMV infection may depend on myriad factors other than the neutralizing antibody maternal response, such as a hypothetical strain-specific tissue tropism for placental filter, the gN-4 variant might require a more efficient neutralization panel to be held in check, because the ORF demonstrates the greatest intragroup variation and may be the most efficient strain for escaping the host immune system and causing the most severe outcomes. This hypothesis is in agreement with reported data [19, 39, 40], showing a strong immune selective pressure to determine genotype clustering both in gN (in particular gN-4, with 4 subgroups) and gO. The immunological significance of viral gene variation may also explain the milder outcomes associated with gN-1 and gN-3a; the possibility cannot be excluded that the 2 variants may be most immunogenic in the mother and/or infant, providing a better protective response. Additional studies are strongly needed to explore this in depth.

Obviously, it would be surprising if the clinical outcome of infection were dependent on a single gene for a virus as complex as CMV. CMV has a strain-specific pathogenic phenotype which could be determined by linked polymorphic genes working in cooperation, as has been hypothesized for the associated loci UL73-gN and UL74-gO [14, 17, 39, 40].

This work attempted to address the demands of families and clinicians by offering a new candidate for the currently available panel of prospective prognostic markers, which may help in defining a differential risk of disease and in management of infected children, which remains a matter of debate. In addition, the present study may open new perspectives for genotyping of viral strains in CMV-infected pregnant women, thereby potentially supporting counseling for families and early intervention for newborns. Additional studies of this topic are strongly encouraged.

This study classified congenitally infected newborns into 2 distinct populations differing in terms of symptoms at birth and sequelae. These 2 clusters demonstrate an array of findings, including these virus-specific gN genotypes, which need to be assembled in a complex puzzle together with other parameters to establish the global risk of developing CMV disease and, therefore, allow more careful management of these infants with regard to family counseling and evaluation of therapy.

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