ORIGINAL ARTICLE

Epidemiological and clinical characteristics of human parvovirus B19 infections during 2006-2009 in Northern Greece

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Abstract

Background. Parvovirus B19 infects children and adults, often causing erythema infectiosum, polyarthritis, but also aplastic crisis in patients with chronic haemolytic anaemia, rash, fever and fetal hydrops or fetal death. This study aims at the detection of acute parvovirus B19 infections during 2006-2009 in northern Greece on epidemiological and clinical aspect.

Material and methods. Specimens were obtained from 63 patients, who addressed to hospitals, suspected for acute parvovirus B19 infection (17 in 2006, 29 in 2007, 10 in 2008 and 7 in 2009). Thirty (47.6%) were children (one day - 15 years old) and 33 (52.4%) were adults (16-65 years old). The infection was shown by PCR in whole blood and/or pleural fluid and supported by detection of specific IgM antibodies in the patients' blood serum, which was performed by ELISA.

Results. Twenty (31.7%) out of the 63 specimens were found to be positive: 3/17 (17.6 %) in 2006, 16/29 (55.2 %) in 2007, none in 2008 and 1/7 (14.3%) in 2009, p=0.0002. Positive children were found 10/30 (33.3%) and positive adults 10/33 (30.3%). Specific IgM antibodies were detected in all 20 positive patients. Children developed hematological disorders, mainly types of anemia (6 cases), hydrothorax/ascites (2 cases), arthritis (1 case), and liver transplant rejection (1 case). Adults were presented with pregnancy complications (2 cases), arthralgia/arthritis (4 cases), febrile syndromes (3 cases) and atypical rash (1 case).

Conclusions. In conclusion, an annual variation in the circulation of parvovirus B19 was noticed, presenting an increase of acute infections in northern Greece during 2007. Regarding serious cases, although children and adults seemed equally affected, differences in clinical manifestations were observed between them, with hematological dysfunctions predominant in childhood. Hippokratia 2011; 15 (2): 157-160

Key words: parvovirus B19, molecular, IgM

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The parvoviruses are small (18-25 nm) viruses with single-stranded DNA genome[1] and are classified in two subfamilies: *Parvovirinae* (vertebrates infection) and *Densovirinae* (insects infection). The *Parvovirinae* subfamily contains three genera: Parvovirus (autonomous replication), Dependovirus (helper-virus supported replication) and Erythrovirus (autonomous replication in erythroid progenitor cells). Humans are mostly infected by parvovirus B19[2].

The most common clinical manifestation in children, especially those aged 4-11 years, is erythema infectiosum causing a "slapped-cheeks" facial rash, extended later on the trunk and limbs and accompanied, in few cases, by fever, headache, coryza, nausea and diarrhoea[1,2]. Joint involvement, transient haemolytic anaemia and encephalitis may also occur. However half of all infections in children are asymptomatic[2]. In adults parvovirus B19 causes polyarthropathy more commonly rather than rash, characterized by symmetrical arthralgia[1-4]. Almost all patients appear with sudden onset, some may present acute anaemia but those with underlying haemolytic disorders may develop transient aplastic crisis. Foetal infection may lead to heavy foetal anaemia causing hydrops foetalis or foetal death, although cases of a non-fatal outcome leaving, however, severe chronic anaemia to some have been reported[1,2].

Laboratory control for parvovirus infection contributes when necessary not only to the differential diagnosis of various clinical pictures in children and adults, but also to the differential diagnosis and manipulation of pregnancy or post-partum incidents.

To our knowledge there has not been conducted a molecular approach - based study regarding acute parvovirus B19 infection in Greece so far. This study is the first on national level to investigate the epidemiological and clinical characteristics of parvovirus B19 infection in cases needing advanced health care.

Materials and methods

Sixty three patients suspected for parvovirus B19 infection, were examined; 17 of them during 2006, 29 dur-

ing 2007, 10 during 2008 and 7 during 2009. Thirty three of the patients were adults (aged 16-65 years old) and 30 were children (one day - 15 years old). The samples were sent to the 2nd Microbiology Laboratory of Medical School by hospitals of Thessaloniki, which cover the needs of northern Greece in serious cases. According to the Greek National Statistic Service this region has a population of about 3 million people, 15% of whom are ≤15 years old.

Adults were investigated for arthralgia/arthritis, febrile syndromes, pregnancy complications, haematological dysfunction, atypical rash or post-transplant complications, while children for anaemia, hydrops, arthritis or post-transplant complications.

Polymerase Chain Reaction technique was used to achieve amplification of a 227 bp DNA segment, part of the Parvo B19 viral gene VP1, in patients' whole blood and/or pleural fluid. Acute infection by parvovirus B19 was proved by detection of the viral DNA. The DNA extraction was performed by QIAamp DNA Mini kit (QIAGEN GmbH, D-40724 Hilden) and the amplification by the use of a homemade protocol[5].

All PCR positive cases were further investigated for parvovirus B19 IgM specific antibodies in blood serum by the use of an immunoenzymatic assay (Serion ELISA classic, virion/serion, GmbH, Germany).

Statistic analysis was performed by the χ^2 method (SPSS, version 15.0).

Results

In a total of 63 cases suspected for parvovirus B19 infection, 20 (31.7%) were confirmed to have been infected by detection of the virus' DNA by PCR and presence of specific IgM antibodies in all 20 patients' blood serum. Only three (17.6%) out of 17 specimens examined in 2006 were found to have been infected by parvovirus B19, while in 2007 16 (55.2%) out of 29 were infected. In 2008 no specimen positive for parvovirus B19 was found among the ten examined and in 2009 only one (14.3%) out of seven (Table 1). A significantly higher frequency of infected cases was noticed in 2007, proved by statistical process (p=0.0002).

Table 1:

Year	Patients examined (Children + Adults)	PCR positive (Children + Adults)	PCR positive %
2006	**17** (7+10)	**3** (2+1)	**17.6** %
2007	**29** (16+13)	**16** (8+8)	**55.2** %
2008	**10** (4+6)	**0**	**0**
2009	**7** (3+4)	**1** (0+1)	**14.3** %
Total	**63** (30+33)	**20** (10+10)	**31.7** %

Results of PCR and IgM antibody detection for Parvovirus B19in patients examined during 2006-2009

Ten (33.3%) out of 30 children cases and ten (30.3%) out of 33 adults were PCR positive. There was no statistically significant difference between the two age groups (p=0.796).

Parvovirus B19 infection caused anaemia to six children, arthritis to one, liver transplant rejection to another one and hydrops to two neonates (including one case with hydrothorax and one with hydrothorax and ascites) while in infected adults caused four cases of arthralgia/arthritis, three of febrile syndromes, two of pregnancy complications (including one foetal death and one foetal hydrops), and one with atypical rash (Table 2).

Table 2:

Clinical syndromes	Children	Adults
Arthropathy	**1**	**4**
Anaemia	**6**	
Fever		**3**
Pregnancy complications		**2**
Hydrothorax/ascites	**2**	
Atypical rash		**1**
Transplant rejection	**1**	

Parvovirus B19 clinical syndromes in children and adultsin patients examined during 2006-2009

Four out of the ten infected adults were pregnant women. In two of them, pregnancy was complicated by the parvovirus B19 infection; one resulting in foetal death, and another in foetal hydrops, as mentioned above. The virus caused no complication to the other two pregnant women, who were however treated/admitted because of arthritis in one case and atypical rash in the other.

Discussion

The present study aimed at the epidemiological and clinical characteristics of parvovirus B19 serious infections in northern Greece during 2006-2009. Despite the rather short studied period and the fact that a study based on hospital patients does not safely reflect the community conditions, an annual variation in the circulation of parvovirus B19 was indicated. Three (17.6%) patients out of 17 were diagnosed in 2006 having parvovirus B19 acute infection by PCR and by the presence of specific IgM antibodies, 16 (55.2%) out of 29 in 2007, none out of 10 in 2008 and one (14.3%) out of seven in 2009. The statistically significant difference (p=0.0002) among them proves that there was an increase of acute infections in northern Greece in 2007 preceded and followed by years of very few or no infections. As it is also reported for other temperate countries[6] as well as in a former study of this same laboratory[17], epidemics are found to occur at intervals of a few years. An important difference in the annual incidence of infection was also observed in Magee-Women Hospital, University of Pittsburgh Medical Center, where 14 cases of infection during pregnancy occurred in 1998, no cases in 1999 and 2000, and 11 cases in 2001[7]. The result of our study opposes the older esti-

mation of B. J. Cohen of two years of epidemic followed by two years of low incidence[3].

In temperate countries, infection with parvovirus B19 is more common among children and presents a lower rate in adults[6,8]. In northern Greece from 2006 to 2009 both adults and children receiving hospital care, seemed equally infected. There were 10/33 adults infected by parvovirus B19 and 10/30 infected children (p=0.796). There is no statistical difference in the two age groups in contrast to previous studies referring to general population and reporting that children are of higher risk of being infected than adults[9,10,17]. Thus it might be resumed that children may be more susceptible to the infection itself, as to numerous infectious agents, however the severity of clinical manifestations does not differ according to age.

Adults and children presented with different clinical manifestations. By studying parvovirus B19 infection from its clinical aspect we concluded that arthritis/arthralgia and febrile syndromes were the most common presentations in adults; four out of the nine adults infected were presented with arthritis/arthralgia, three with febrile syndromes, while two with pregnancy complications and one with atypical rash. In B.J. Cohen's study in 1995, arthritis was also more frequently seen in adults, especially women, than in children[3]. Moreover I. Colmegna et al. report that joint complains occur more often in adults and that they are usually presented as a symmetric polyarthritis affecting the small joints of the hands, wrists and knees[3,6,8,12]. In our study adults with arthritis did not manifest a rash, confirming the fact that this is a common presentation of parvovirus B19 infection in adults[3].

Febrile syndromes were, as mentioned above, as common as arthritis. Besides, most cases of infection with parvovirus B19 in healthy adults are either asymptomatic or characterized by mild, non-specific, cold-like syndromes[8,12].

Although parvovirus B19 may cause acute cessation of the red blood cells production, there was no case of adult anaemia, caused by parvovirus B19, in this study. Non-immunocompromised patients remain mostly asymptomatic[12]. Transient aplastic crisis and chronic anaemia are developed in patients with illnesses that shorten red blood cells' life, such as sickle cell anaemia, thalassaemia and in immunodeficient patients respectively[3,6,8,12]. None of the adult patients examined in this study had a background of immunodeficiency or haemospherinopathy.

Four of the nine (44.4%) infected by parvovirus B19 adults were pregnant women. Reports about the percentage of pregnant women that develop symptoms attributable to parvovirus B19 infection vary in different parts of the world[7]. The infection caused pregnancy complications to two of the four infected pregnant women of this study. The other two, one appearing only with arthritis and the other with an atypical rash during the infection, finally delivered healthy infants. Pregnant women with asymptomatic infection are at greater risk to develop pregnancy complications - such as hydrops foetalis and foetal death - especially if the infection occurs in the first and second trimester[3]. There was one case of foetal death reported to us and one of foetal hydrops. The risk of foetal loss due to parvo B19 infection in international bibliography varies up to 16% [3,7,13], while a recent study in the U.S.A. reports that 12% of the infected foetuses develop hydrops[7].

There are reports in Italy and Belgium of parvovirus B19 detection in gastric and intestinal mucosa and association of the infection with a severe inflammatory bowel disease[5,14]. Nevertheless none of our patients developed such symptoms.

Children presented mainly haematological dysfunctions, as there were six (four neonates and two infants) out of ten children with anaemia. Most of the children that appeared with symptoms in this study were maternally infected, as assumed by their age together with the fact that anaemia was their prevailing clinical manifestation. Infection with parvovirus B19 during pregnancy may result in the reduction of the red blood cell production and the development of severe congenital anaemia[8].

Two out of ten infected by parvovirus B19 children, both neonates, presented with hydrothorax and ascites, which are presentations of hydrops that infection via the placenta may also cause.

One out of the ten infected children suffered from arthralgia. We may notice, once more, that arthritis can be observed in children but not as a common symptom of infection as in adults.

Transplant recipients are at high risk of developing symptomatic parvovirus B19 infection due to their immunodeficiency[9]. It has been estimated by J.B. Park et al that 84 out of 143 kidney-transplant recipients (58.7%) showed at least one PCR positive[16]. Our one case of child liver-transplant recipient infected by parvovirus B19 resulted in the rejection of the transplant. There is probably a connection between this fact and the role of B19 viral non-structural protein, NS1, which, according to a study of Brian D. Poole et al, induces apoptosis of liver cells[10].

Since infectious diseases are at present the best explained pathologic conditions, it is important for the international scientific community to be aware of the expansion and presentation of the infectious agents in a region, in a country or in neighbouring ones. The attraction of the attention of clinicians to as many infectious agents as possible is basic for a good monitoring of the correspondent diseases and finally for a sufficient control and prevention of any target-agent selected.

References

1. Knipe DM, Howley PM, editors. Fields Virology. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2001.
2. Zuckerman AJ, Banatvala JE, Pattison JR, Griffiths PD, Schoub BD, editors. Principles and Practice of Clinical Virology. 5th ed. West Sussex: Wiley; 2004.
3. Cohen BJ. Parvovirus B19: an expanding spectrum of disease. BMJ. 1995; 311: 1549-1552.
4. Colmegna I., Alberts-Grill N. Parvovirus B19: its role in chronic arthritis. Rheum Dis Clin North Am. 2009; 35: 95-110.

5. Kyriazopoulou V, Simitsopoulou M, Bondis J, Diza E, Athanasiadis A, Frantzidou F, et al. Human parvovirus B19: Immunity of Greek females and prenatal investigation of hydrops fetalis. Eur J Obstet Gyn R B. 1997; 74: 157-160.
6. Mossong J, Hens N, Friedrichs V, Davidkin I, Broman M, Litwinska A, et al. Parvovirus B19 infection in five European countries: seroepidemiology, force of infection and maternal risk of infection. Epidemiol Infect. 2008; 136: 1059-1068.
7. Beigi RH, Wiesenfeld HC, Landers DV, Simhan HN. High rate of severe fetal outcome associated with maternal parvovirus B19 infection in pregnancy. Infect Dis Obstet Gynecol. 2008; 2008: 524601; PMID: 18464909.
8. Servey JT, Reamy BV, Hodge J. Clinical presentations of parvovirus B19 infection. Am Fam Physician. 2007; 75: 373-376.
9. Marchand S, Tchernia G, Hiesse C, Tertian G, Cartron J, Kriaa F, et al. Human parvovirus B19 infection in organ transplant recipients. Clin Transplant. 1999; 133: 17-24.
10. Poole BD, Zhou J, Grote A, Schiffenbauer A, Naides SJ. Apoptosis of liver-derived cells induced by parvovirus B19 nonstructural protein. J Virol. 2006; 80: 4114-4121.
11. De Oliveira SA, Bastos Camacho LA, Fernandes Bruno L, de Gusmão RC, de Medeiros Pereira AC, Coca Velarde LG, et al. Acute arthropathy in patients with rash diseases: a comparative study. Clin Rheumatol. 2009; 28: 1067-1071.
12. Frotscher B, Salignac S, Morlon L, Bonmati C, Jeulin H, Venard V, et al. Neutropenia and/or thrombocytopenia due to acute parvovirus B19 infection. Ann Biol Clin. 2009; 67: 343-348.
13. Hawkins AE, Killam IW, Gold R, MacDonald NE, Halperin SA, Lapointe N, et al. Erythema infectiosum and parvovirus B19 infection in pregnancy. CMAJ. 1988; 139: 633-634.
14. Fremont M, Metzger K, Rady H, Hulstaert J, De Meirleir K. Detection of herpesviruses and parvovirus B19 in gastric and intestinal mucosa of chronic fatigue syndrome patients. In Vivo. 2009; 23: 209-213.
15. Pironi L, Bonvicini F, Gionchetti P, D'Errico A, Rizzello F, Corsini C, et al. Parvovirus B19 infection localized in the intestinal mucosa and associated with severe inflammatory bowel disease. J Clin Microbiol. 2009; 47: 1591-1595.
16. Park JB, Kim DJ, Woo SY, Choi GS, Chum JM, Jung GO, et al. Clinical implications of quantitative real time-polymerase chain reaction of parvovirus B19 in kidney transplant recipients - a prospective study. Transpl Int. 2009; 22: 455-462.
17. Kyriazopoulou VG, Exindari MK, Gerakari TA, Manatakis DK, Noutsou FN, Melidou AV. Distribution of Human parvovirus B19 in Northern Greece during 1995-2003. Acta Microbiol Hell. 2005; 50: 165-169.