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The burden of pediatric HIV/AIDS in Costanta, Romania – a cross-sectional study

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Title: The Burden of Pediatric HIV/AIDS in Constanta, Romania: a Cross-sectional Study

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Abstract

Background: By 1990, 94 percent of the acquired immunodeficiency syndrome (AIDS) cases in Romania were in children less than 13 years of age. The majority of the cases were identified in Constanta. The purpose of this paper was to describe the current burden of pediatric human immunodeficiency virus (HIV) infection in Constanta, Romania.

Methods: A cross-sectional study was designed to address the primary objective. Between April 1999 and March 2000, all living cases of pediatric HIV infection in Constanta were identified. Standard demographic, social, clinical, treatment and hospitalization data were collected for each study subject. Data were analyzed according to cross-sectional study design methodology.

Results: Of the 762 subjects, the majority were seven to 11 years of age, lived with their parents and attended school. Only 70% of the fathers and 13% of the mothers were employed. Horizontal transmission accounted for 90% of the cases. Most of the children had moderate to severe disease as indicated by their AIDS-defining signs; 40% had AIDS. Less than half of the children were receiving antiretroviral therapy (ART). ART and children of mothers with a high school or greater education were independent predictors of long-term non-progression of HIV disease.

Conclusions: This cross-sectional study demonstrated that ten years after the HIV epidemic was

identified in Romania, it remains a health and economic burden. The infected children are very ill, but ART is not available for all. The proportion with vertical transmission has increased from an estimated four % to nine %. Our findings support the need to get HIV therapy to economically challenged countries such as Romania.

Background

Through November 1989, Romania had reported 13 cases of the acquired immunodeficiency syndrome (AIDS) to the World Health Organization (WHO). After the collapse of the Communist regime in Romania in December 1989, there were reports of large numbers of children with human immunodeficiency virus infection (HIV) and AIDS[1]. In early March 1990, the Centers for Disease Control and Prevention was invited to provide epidemiological assistance to establish a national AIDS surveillance system[2]. In its first report of AIDS cases, the Romanian Ministry of Health reported that 77% of cases were from only five of Romania's 41 districts. The Constanta district which includes Constanta, a major port on the Black Sea, had 426 cases; Bucharest, the capital of Romania, had 189 cases; Giurgiu, located on the Danube River where virtually all traffic to Bulgaria from Bucharest passes through, had 119 cases; Bacau, in Moldavia, had 87 cases; and, Galati, also a port on the River Danube, had 74 cases. The majority of the cases (94%) were in children less than 13 years of age and resulted from indiscriminate injections with contaminated needles and syringes[3]. Only a small percentage (4%) of the pediatric cases resulted from vertical infection.

The most recent global report by the Joint United Nations Programme on HIV/AIDS (UNAIDS) reports, in 2000 alone, 5.4 million people were newly infected with HIV, of which 620 000 were children less than 15 years of age. An estimated 5 000 children in Romania were living with HIV/AIDS in 1999. The city of Constanta remains the epicenter of pediatric HIV/AIDS in both Romania and Eastern Europe. The purpose of this study was to conduct a population-based cross-sectional study to describe the current burden of pediatric HIV infection in Constanta, Romania.

Methods

The study was conducted at the Municipal Hospital in the city of Constanta, Romania. The infectious diseases medical staff cares for all children who seek care for and are diagnosed with HIV infection. The Municipal Hospital has both inpatient and outpatient facilities for children and adolescents with HIV infection. The inpatient area can accommodate up to 65 children and adolescents. The outpatient clinic operates twice per week and sees approximately 20 to 25 patients per session. The majority (97%) of the HIV-infected children seen at Municipal Hospital in Constanta are from Constanta county. The remaining three % of cases are orphaned or abandoned children from other areas of Romania.

The 1997 population of Constanta county was 746 700. The child population, zero to 15 years of age, was 161 287. The city of Constanta, in Constanta county, is located on the eastern boarder of Romania and is an important shipping port on the Black Sea. The 1999 population was estimated at 339 250 and the child population, zero to 19 years of age, was 88 205.

The cross-sectional study population consisted of all living HIV-infected infants, children and adolescents, zero to 18 years of age and known to the medical staff at the Municipal Hospital between April 1999 and March 2000. There is no systematic surveillance for HIV in Constanta nor are high-risk pregnant women tested. The majority of newly identified cases are tested for the HIV virus and diagnosed when those individuals seek medical care, usually for an HIV-related illness. Thus, the study population is not complete, i.e. all prevalent cases in Constanta have not been identified. Estimates, however, are at least 90-95% of pediatric cases that have been identified and are most likely representative of all the prevalent cases.

A standard data collection form was completed for each case that met the study's inclusion criteria. The form included demographic, social, HIV risk factor, clinical, treatment

and hospitalization data. The Center for Disease Control and Prevention's 1994 revised classification system for human immunodeficiency virus infection in children less than 13 years of age was used to determine the clinical category[4]. This system provides mutually exclusive states based on the intersection of four clinical and three immunological categories. Due to the resource-limited environment at the Municipal Hospital in Constanta, CD4-positive cell counts are not available. As a result, the immunological categories were not used to describe the population. Clinical categories classify children with no (category N), mild (category A), moderate (category B) or severe (category C) AIDS-defining signs. Medical record abstraction was the primary method for data collection. For the purposes of this descriptive review of study subjects, long-term non-progressors (LTNP) were defined as those children eight years of age and older and classified in the CDC clinical category A.

The data are maintained in a database created with Microsoft Access. Statistical analyses were performed with the SAS software. Descriptive statistics were used to describe the population and Chi-square analysis was used to test for differences between groups. Logistic regression was used to determine independent factors associated with LTNP while controlling for other factors.

This study was approved by the Baylor College of Medicine Institutional Review Board for Human Subject Research and by a Single Project Review Committee for Human Subject Research in Romania and the Romanian Ministry of Health.

Results

Data collection forms were completed for 762 pediatric cases of HIV infection ranging from zero to 18 years of age. The demographic and social characteristics of the study population

provide great insight to the current pediatric HIV/AIDS population in Constanta (Table 1 here). The majority of the study subjects are seven to 11 years of age, of Romanian (Caucasian) ethnicity, and live with their parent(s) or a relative. Most of the children are well enough to attend school. Parental education was commonly stopped before receiving a high school degree. Seventy percent of the fathers reported employment whereas only 13% of the mothers were employed outside of the home.

The mode of transmission of HIV was primarily through transfusions and other medical practices via contaminated needles and syringes (Table 2 here). These medical procedures were conducted usually during the first year of life. Perinatal transmission accounted for nine % of the cases. Of the perinatal transmission cases, their dates of birth range from 1987 through 1998.

The children seek medical attention many years after their infection with HIV, thus their mean age at diagnosis is eight and one-half years. The majority (82%) of children have moderate to severe disease as indicated by their AIDS-defining signs; 306 (40%) are diagnosed with AIDS. The most prevalent conditions for the children categorized in the CDC clinical category A were lymphadenopathy (100%), hepatomegaly (97%) and recurrent or persistent upper respiratory infection, sinusitis or otitis media (97%). For children categorized in the CDC clinical category B, most had been diagnosed with a single episode of bacterial meningitis, pneumonia or sepsis (95%), candidiasis (68%), chronic or recurrent diarrhea (52%), lymphoid interstitial pneumonia (50%) or recurrent herpes simplex virus stomatitis. Those children in the CDC clinical category C suffered from multiple or recurrent serious bacterial infections (97%), wasting syndrome (69%), encephalopathy (51%), esophageal or pulmonary candidiasis (47%) or herpes simplex virus (39%). Cancer, Kaposi's sarcoma or a lymphoma, had been diagnosed in nine (1%) of the 762 children.

Less than half of the children are receiving antiretroviral treatment. For those receiving antiretroviral therapy, it was started at a median age of 10.4 years (range: 1.3-18.2). PCP chemoprophylaxis was initiated at a median age of 7.4 years (range: 0.4-16.0). At some time after their diagnosis of HIV, 96 (13%) of the study subjects had been hospitalized. The primary discharge diagnoses for the majority of hospitalizations were tuberculosis and encephalopathy.

One hundred and twenty-seven (17%) children were defined as LTNP (CDC category A and \geq eight years of age). Several factors were associated with LTNP including inverse associations with birth weight and maternal education and a positive association with current antiretroviral therapy (Table 3 here). The results of a logistic regression model which included these three independent dichotomous variables indicated that the children of mothers with less education were 2.7 times more likely not to be a LTNP (95% CI 1.6-4.5) and children not on antiretroviral therapy to be 1.6 times more likely not to be a LTNP (95% CI 1.01-2.6).

Conclusions

Factors associated with the 1989-90 pediatric HIV epidemic in Romania have been reported. Because most of the HIV infected children were born to uninfected mothers, HIV transmission was presumed to be related either to transfusion of unscreened blood or blood products, or to the re-use of unsterilized needles and syringes[3, 5]. This study describes the current HIV-infected child and adolescent population in Constanta; the majority of whom were infected during the 1989-1990 epidemic. As a whole, these 762 children and adolescents who are representative of pediatric HIV/AIDS in Constanta present a striking burden on the medical resources in Constanta. Because the majority are in the moderate to severe stage of their HIV infection, they require significant medical attention.

Antiretroviral therapy has been available in Constanta since 1996; triple therapy became available in 1998. Children with chronic encephalopathy and psychomotor retardation are not placed on therapy nor are children with contraindications. Very few parents refuse antiretroviral therapy. In this study, however, only 43% were on some type of drug regimen for HIV. As a result of the economic burden of HIV therapy, not all children have the opportunity to receive drug therapy for their HIV.

Under several provisions, the governmental budget from the Minister of Health covers the cost of antiretroviral therapy for HIV for some but not all children. Antiretroviral therapy is usually covered for a total of 500 children in Constanta. There are periods of time, however, when the National Health Security House does not have the funds to cover the costs of therapy for all 500 children. Recently, the lack of funds resulted in stopping treatment for approximately 100 children in Constanta. Antiretroviral therapy for the orphans and abandoned children in Romania is categorized as social assistance. Thirty percent of this social assistance is covered by the budget of the Minister of Health and seventy percent is covered from other sources, such as NGOs, The European Community and UNICEF. It is clear, as with other resource poor nations, that there is inadequate funding for antiretroviral therapy for Romanian children[6].

In contrast to the 1989-1990 epidemic, a large proportion of the currently infected children and adolescents are living with their parents or relatives rather than in orphanages. The majority of the children who were in orphanages in 1989-1990 remain abandoned in the hospital or in family houses. Some children have been placed in foster families through the support of governmental or NGO support.

Social factors relating to the child's place of residence, such as mother's level of education, are independently associated with disease progression in this population. Of interest

were the older children who remained categorized in the CDC clinical classification of A and defined as long-term non-progressors. A logistic regression model indicated that children and adolescents whose mothers had attained at least a high school degree and were currently on antiretroviral therapy were more likely to be a LTNP than children of mothers with less education and/or not currently on antiretroviral therapy.

It is unfortunate that perinatal transmission has increased since the early 1990s. Nine percent of the study population's direction of transmission was vertical. Prostitution is a major factor associated with this increase of vertical transmission. The majority of the HIV infected women in Constanta were infected by sexual transmission. As noted by Stephenson in her perspective on HIV/AIDS surging in Eastern Europe, "increased poverty, unemployment, an ailing public health system, and other manifestations of socioeconomic turmoil have fostered drug use, an increase in prostitution, and epidemics of sexually transmitted disease – which, in turn, increase the spread of HIV"[7].

Romania has a national HIV prevention program in which each county develops county specific materials. The county of Constanta has developed a program. Evaluations of this program are not available. From the results of this study, it is imperative that young females be targeted. The reduction in cases of pediatric HIV in Romania will not occur without the reduction in perinatal transmission. In addition, the prevention programs must target those that have not had the opportunity to attain at least a high school education.

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Table 1. Demographic and social factors of HIV infected children and youth
Constanta, Romania 1999 – 2000

Demographic Factors			Social Factors		
	N	%		N	%
Gender			School		
Male	426	(56%)	Yes	615	(81%)
Female	336	(44%)	No	135	(18%)
			N/A	12	(1%)
Ethnicity			Father Education		
Romanian	614	(81%)	<HS	439	(78%)
ROM*	45	(6%)	HS	91	(16%)
Turkish/Huns	94	(12%)	>HS	33	(6%)
Other	6	(1%)			
Age (yrs)			Mother Education		
0-6	16	(2%)	<HS	472	(81%)
7-11	581	(76%)	HS	85	(15%)
12-18	165	(22%)	>HS	23	(4%)
Residence			Father Employed		
Parent(s)	599	(78%)	Yes	396	(70%)
Relatives	28	(4%)			
Orphanage	122	(16%)	Mother Employed		
Hospital	13	(2%)	Yes	78	(13%)

*ROM=gypsy

Table 2. Clinical factors of HIV infected children and youth, Constanta, Romania 1999 –

2000		
Clinical Factors	N	%
Transmission		
Perinatal	72	(9%)
Transfusion	231	(30%)
Parenteral	459	(60%)
Year of Diagnosis		
90-92	270	(35%)
93-94	149	(20%)
95-97	231	(30%)
98-99	112	(15%)
Age at Diagnosis		
Mean (SD)	8.5	(2.1)
CDC Clinical Category		
A	135	(18%)
B	320	(42%)
C	306	(40%)
AIDS		
Yes	306	(40%)
Antiretroviral therapy		
Yes	325	(43%)

PCP chemoprophylaxis

Yes	540	(71%)
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Hospitalization for HIV disease

Yes	96	(13%)
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Table 3. Relationship of factors with LTNP* in study subjects 8 years of age or older

<u>Factor</u>	<u>LTNP</u>	<u>Not LTNP</u>	<u>p-value</u>
<u>Birthweight</u>			
≤2500	8 (7%)	94 (17%)	0.01
<u>Gender</u>			
Male	57 (49%)	309 (57%)	0.12
<u>Maternal education</u>			
<high school degree	63 (64%)	401 (85%)	0.00
<u>Current ART**</u>			
Yes	65 (51%)	229 (37%)	0.01

*LTNP = long-term non-progressors

**ART = antiretroviral therapy

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Reviewers' reports

The burden of pediatric HIV/AIDS in Costanta, Romania – a cross-sectional study

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Francois Dabis

General comment: This is the most recent study describing the burden of pediatric HIV/AIDS in Romania, the country with the heaviest toll in Europe. The authors have attempted to make the best use of available data in the region of Constantia to provide an estimate of the magnitude of the problem and plea for improved case management through adequate services including antiretroviral treatment. The

paper is reasonably well written, the limitations are well delineated. Some of them may be addressed however in a revised and improved version of the manuscript before publication.

Specific comments:

Abstract: Methods section should state how cases were identified. Second sentence of the conclusion is excessive as no denominator and therefore rate per population-unit is provided.

Background: Second paragraph: I think prevalence figures for children would be more useful than incidence as the issue in Romania appears to be the burden of cases, not the velocity of the pediatric HIV infection.

Methods:

. I am not sure (first sentence, as well as last sentence of the Background section) that this is really a community-based assessment. It is hospital-based rather than anything else. Third paragraph: I am concerned by the diagnosis of pediatric HIV infection below 18 months of age, the authors do not tell us what they do in this situation. What is in fact the case definition used in this study ?

. If I understand correctly, this is a prevalence for a given period, based on all children seen at least once in a hospital. The last sentence of this third paragraph on the representativeness and the coverage is not well documented for this purpose.

. Fourth paragraph: The fact that medical record abstraction was the primary method of data collection does not tell how the records of those lost to follow-up were handled.

Results:

- . First paragraph, first sentence: were some cases meeting the inclusion criteria excluded from the analysis ? if yes, for which reason(s)?
- . Second paragraph: how was the mode of transmission ascertained ? What was the definition of a perinatally-acquired infection ?
- . Third paragraph: I assume you provide here cumulative figures of the occurrence of clinical events over time rather than prevalence figures at the time of the survey. This requires clarification.
- . Last paragraph: The fact that only half of the children received ARV is a concern but one needs to know how many were truly eligible based on international criteria at the time of the survey. The two factors that remain associated with the lack of clinical progression are by no means of the same level of interest. This is insufficiently discussed in the Conclusions.

Conclusions:

- . This is in fact a discussion, which is perfectly legitimate.
- . First paragraph, sentence before last: To assess the burden on the system, one would need to know the rate for the county / state or for the city, for the overall population or even better per 10,000 or 100,000 under the age of 20.
- . Second paragraph: again, the issue of the eligibility criteria for ARV is not discussed at all.
- . Fourth paragraph: another way to document the burden of the problem would be to know how many children already diagnosed as HIV-infected or suspected to be infected died in the 90's in Constantia.
- . Paragraph before last, it is unclear whether the vertical transmission has increased or if diagnostic procedures have improved and the proportion of horizontal transmission has - hopefully - decreased over time. This deserves some discussion.
- . Last paragraph: I would argue that proper case management of the already infected children that are diagnosed or can be diagnosed is per se a priority action for Constantia as the burden of disease is already there.

Tables

- . Table 1: use the same age categories in this table and in the prognostic study of disease progression. Is it possible to know the serostatus of the parents
- . Table 2: It would be worth knowing the circumstances and age at diagnosis in addition to the year of diagnosis. I assume that AIDS, ARV, PCP prophylaxis and hospitalization correspond to what has been documented at any point in time, not simply at the time of the survey.

Competing interests

None declared

B Eley

The study by Kozinetz and Matusa represents another episode in the unfolding Romanian paediatric HIV epidemic. Attention was focused on Romania in 1990 when the Romanian HIV epidemic was first discussed in the English medical literature (Lancet 1990;335:672). The state of the epidemic at the end of 1990 was described in a prospective, descriptive study published in the Lancet (Lancet 1991;338:645-649). By December 1990 1168 HIV-infected individuals were reported to the Romanian Ministry of Health and of these 1094 (93.7%) were children. Four hundred and twenty three (38.7%) acquired their infection from contaminated blood transfusions, 6 (0.5%) from other blood products

administered for clotting disorders and 37 (3.4%) by vertical transmission. In the remaining 628 children (57.4%) the cause of infection was unknown but probably resulted from exposure to contaminated needles and or syringes.

To address the major causes of the epidemic the Ministry of Health developed guidelines for blood transfusion, HIV screening was introduced at blood centres countrywide, health care workers were encouraged to prescribe oral medication instead of parenteral therapy and plans were discussed to produce disposable needles and syringes. What has happened to the paediatric epidemic since then? Kozinetz and Matusa provide us with current information about the state of the paediatric epidemic in the Constanta District, the epicentre of the paediatric epidemic in Romania.

This is an important follow-up study of general medical and scientific interest. However, the authors should take into consideration the following concerns and comments when finalising their paper for publication.

Concerns / comments

1. The variable use of the terms Constanta, Constanta District, City of Constanta and Constanta County make the manuscript somewhat difficult to follow. Could the use of these terms throughout the manuscript be revised and simplified. To bring greater clarity to the manuscript, perhaps only the terms "city of Constanta" and "Constanta district" should be employed.

2. Background

The second last sentence in paragraph 1 is somewhat misleading. It should read: " The majority of cases (94%) were children less than 13 years of age. Contaminated blood products and indiscriminate injections with contaminated needles and syringes were the main sources of infection in children."

Second sentence in paragraph 2: Could the authors please provide a reference for the 1999 paediatric estimate.

3. Methods

Except for the first sentence, most of the first paragraph describes activities at the Municipal Hospital and should therefore be omitted from the methods section. With exception of the last 2 sentences, which probably belong in the results section, most of this paragraph should be considered for inclusion in the discussion.

Paragraph 2 describes the population size in the city of Constanta and Constanta district. This paragraph should not be included in the methods section. Perhaps some of this information may be included in the background or the discussion.

Paragraph 3: The last 2 sentences probably belong in the discussion. If the last sentence is included in the discussion, could the authors please provide a reference for this estimate?

Could the authors please include the definitions of the modes of transmission (transfusion, parenteral, refer Table 2) in the methods section. For example, in table 2 does transfusion refer to blood transfusions only or all blood

products? What does the term parenteral in table 2 refer to – use of contaminated needles? Syringes? Surgical instruments?

Paragraph 4: Could the authors please clarify the definition of the term “long-term non-progressor”. As it currently stands any HIV-infected child 8 years or older with category A features may be included irrespective of the timing of transmission e.g. a child who acquired his or her infection at age 6 years may be included at age 9 years if he / she has category A disease. Perhaps LTNP means “any child with category A disease who has had HIV infection for more than 8 years” ? Could the authors please comment and revise the definition accordingly.

4. Results

Could the geographic origin of the patients be included in this section, i.e. the percentage of children residing in the Constanta district and the percentage living in other districts of Romania.

Could the authors please include the mean age \pm standard deviation of the whole cohort.

Could the authors include an analysis of when transmission occurred i.e. the percentage of transmission before and after 1990 and give a break down in terms of the mode of transmission. This is important because as the manuscript stands, there is no discussion on whether the proposed improvements of health care practices (recorded in the Lancet publication: Lancet 1991;338:645-649) were actually implemented and whether transmission from blood products and contaminated implements consequently declined after 1990.

Paragraph 3, sentence 3: The “most prevalent conditions” should be changed to the “most prevalent clinical features”.

5. Discussion (= conclusion)

Could the authors please discuss what changes to medical practice were implemented after 1990 and whether these changes had a positive impact on the paediatric epidemic and pattern of transmission in Constanta.

Please provide a bit more insight into the management of children treated with antiretrovirals. For example, it was stated in the methods section that CD4 cell monitoring is not done in Romania. Are viral loads monitored? How is the effect of antiretrovirals determined – on clinical grounds

6. Quality of English

Reasonable but should be improved for greater clarity.

Competing interests

None declared