Paediatric HIV: The Experience in Ireland 2004-2011

Abstract:

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Abstract
Despite effective prevention strategies paediatric HIV infection remains an important condition in Ireland. To characterise presentation and identify barriers to optimal management a retrospective chart review of HIV-infected children presenting in Ireland, 2004-2011 was undertaken. Forty-two HIV-infected children were identified; (25 male). Median age at presentation was 6 years (range 0-16 years). 38 children (90%) were born to African mothers. Eleven (26%) were born in Ireland. Twenty-five (59%) were late diagnoses; 11 were symptomatic. Ten of 12 foreign born HIV-infected children had antiretroviral exposure with frequent resistance associated mutations. Seven of 8 children with stage C disease had previously been admitted to hospital in Ireland before diagnosis. Maternal non-adherence to recommendations and seroconversion in pregnancy challenge the goal of paediatric HIV eradication. Targeted strategies for women at risk of infection in pregnancy are required. Late HIV diagnosis remains common, highlighting the need for a more proactive approach to HIV testing.

Introduction

The epidemiology of paediatric HIV infection in Ireland has changed considerably since the first child was diagnosed in Ireland in 1985. Initial studies reported that most infected children were born to Irish women with intra-venous drug use (IVDU) related infection. The vertical transmission rate (VTR), at 12-15%, was at the lower end of the reported range[1,2]. This low transmission rate was attributed to the fact that this was primarily a non breast-feeding population, in the relatively early stages of the HIV epidemic. Thereafter, coupled with the economic upturn of the mid to late nineties, Ireland experienced a marked increase in immigration, particularly from sub-Saharan Africa. In the absence of interventions, a VTR of approximately 30% might have been anticipated in this largely African breast-feeding population[3]. Fortunately, these demographic changes coincided with the roll out of routine antenatal testing and the introduction of the Irish programme for prevention of mother to child transmission (PMTCT) of HIV in 1998 - 1999. There followed a reduction in the vertical transmission rate to <1%[4]. Despite this success, HIV-infected children continue to present for care and new infections, often at an advanced stage, are diagnosed each year. This study sought to characterise the current modes of presentation of HIV-infected children in Ireland in order to highlight the continuing importance of HIV infection as a diagnostic consideration, even in this era of effective prevention, and to identify barriers to the early diagnosis and optimal management of infected children.

Methods

The Rainbow Clinic at Our Ladyâ s Childrenâ s Hospital, Crumlin and the Childrenâ s University Hospital, Dublin is the national referral centre for all HIV-infected children in the Republic of Ireland. A retrospective chart review of all HIV-infected children who presented between 2004 and 2011, inclusively, was undertaken. Children were categorised by place and timing of diagnosis. Group 1 included children diagnosed prior to arrival in Ireland; Group 2, infants born to mothers known to be HIV positive and diagnosed during postnatal monitoring i.e. â early diagnosisâ ; Group 3, all other infants and children diagnosed in Ireland, i.e. â late diagnosisâ . The CDC classification of Paediatric HIV infection was used[5]. Data collected on a standardized data sheet included; demographics, duration of residence in Ireland, hospitalisations in Ireland prior to HIV-diagnosis, antiretroviral (ARV) exposure history, clinical presentation, CDC stage, co-infections, CD4 count, viral load and resistance associated mutations.

Results

Forty-two HIV-infected infants and children were identified; 25 male and 17 female. The median age at presentation was 6 years (range 0-16 years). Overall 90% (38/42) were born to African mothers; 69% (29) in Africa. HIV transmission was vertical in 90% (38/42), horizontal in 5% (2) and unknown in 5% (2). Seventy-one percent (30) of children were newly diagnosed at presentation. The characteristics of each group are listed in Table 1.

Group 1: Children diagnosed prior to arrival in Ireland

Twelve children had been diagnosed with HIV prior to arrival in Ireland; 10 in Africa, and two in Europe. Ten of 12 children (83%) were receiving or had previous exposure to ARVs at the time of presentation; 5 were on highly active antiretroviral therapy (HAART) of whom 3 were virally suppressed. Five, off treatment, had prior ARV exposure (1 HAART, 2 dual or monotherapy, 2 infant post exposure prophylaxis (PEP)). Of the 10 patients with ARV exposure, 6 of 7 with detectable viremia had baseline resistance testing. Three, each with prior HAART exposure, had detectable resistance associated mutations, (K103N, Y181C, M184V, M41L, T215Y). Two children were ARV naˆfIve. The history of prior diagnosis and/or ARV exposure was not always immediately disclosed, leading to delay in initiation of appropriate ARV therapy in one case. Two children had tuberculosis. There were no co-infections with hepatitis B or C.

Group 2: Infants diagnosed during prospective postnatal monitoring (early diagnoses)

Five Irish born infants were diagnosed â earlyâ as part of the routine postnatal monitoring of HIV-exposed infants. In 4 of 5, HIV-RNA was detected on day 1 of life confirming in-utero transmission. Maternal diagnosis was made following delivery for one infant and in association with third trimester seroconversion at 38 weeks gestation for another. Failure to take prescribed antenatal ARVs accounted for transmission in 2 additional infants. The fifth infant was delivered vaginally to a HAART recipient with viraemia of <200 cpm, but who had a small antepartum haemorrhage at delivery. In this infant HIV RNA, not detected at birth, was detected for the first time on day 23 of life, suggesting perinatal transmission despite intrapartum intravenous zidovudine and neonatal triple therapy prophylaxis. Resistance mutations were not detected in the motherâ s samples, however M184V was detected in the infant on day 31 of life. No other infant had resistance associated mutations detected.

Group 3: All other HIV-infected children diagnosed in Ireland (late diagnoses)

Twenty-five (59%) HIV-infected children were late diagnoses; 11 were symptomatic, 11 followed diagnosis in another family member and 3 were diagnosed as part of a voluntary screening programme for asylum seekers. Six children were the index case within the family. Five children had asymptomatic co-infections: Hepatitis B, 3; and latent tuberculosis, 2. There were no cases of hepatitis C or congenital syphilis. Six Irish-born infants were diagnosed late. Three infections were associated with maternal seroconversion in pregnancy; one infant was born prior to introduction of routine antenatal testing and one to a mother who refused antenatal testing. In one child the source and timing of infection remains unclear. Nineteen foreign-born children were newly diagnosed in Ireland. The median time to diagnosis after arrival in Ireland was 1.6 years (range 0.02 â 6.6 years), with a significant minority (4/19) living in the country for 4 or more years prior to diagnosis.Nine of the 25 (36%) late diagnoses had a previous hospital admission in Ireland. Seven of 8 children with CDC stage C disease, clinical AIDS, had previously been hospitalised in Ireland prior to diagnosis. Seventeen children had baseline resistance testing. No significant resistance associated mutations were detected in this group.

Discussion

The arrival of HIV-infected children from Africa who have been exposed to ARVs, increasing numbers of whom are receiving or have previously received HAART, is a relatively new phenomenon and presents new challenges. While the increased availability of ARVs is a welcome development, history of prior treatment is not always disclosed and treatment may have been intermittent or non-suppressive, all of which can increase the risk for ARV resistance. In this review, half of the children diagnosed prior to arrival who had been exposed to HAART were not virally suppressed and almost one third of those had resistance associated mutations, illustrating the importance of baseline resistance testing. In contrast, consistent with prior reports,[6] viral resistance was not detected amongst the ARV-naive children, suggesting that, as yet, transmitted resistance in the paediatric population remains uncommon.

The routine programme for prevention of mother to child transmission of HIV in Ireland involves opt out antenatal HIV screening, antenatal and infant postnatal ARV treatment and intravenous intrapartum ARV as necessary[7]. Despite the success of this prevention programme a low level of residual transmission persists. Maternal seroconversion in pregnancy has emerged as an important cause of infection and often delayed HIV diagnosis[8,9]. Four of 10 Irish-born children, diagnosed after establishment of routine antenatal testing, were infected in association with documented maternal seroconversion in pregnancy. A call for repeat routine HIV testing in pregnancy has been made[10], the case for which is strong in high incidence areas. However, a recent Irish economic evaluation found that the cost of introduction of repeat universal routine antenatal HIV screening in the third trimester is high compared to expected benefits.[11] Similarly, in 2009, the UK antenatal screening review committee concluded that routinely offering a second test to all pregnant women is not justifiable. Instead they recommended focusing efforts on implementation of current policies, maximising initial test uptake, and that repeat testing should be readily available on maternal request[12]. Notably in this study, only one of four mothers who seroconverted requested a repeat test.

In general, selective screening programmes have not met with great success. We are therefore faced with the challenge of developing appropriate interventions for this group. Population based educational programmes on benefits of HIV testing and the importance of adherence to recommendations must be coupled with targeted interventions aimed at those at ongoing risk of transmission. Where universal repeat testing in late pregnancy or delivery is not justified, it is important to raise awareness of the need for repeat testing in those at risk e.g. serodiscordant partner, continuing intravenous drug use, from high prevalence community, and to ensure that such testing is readily available on request. Despite the success of PMTCT programmes, HIV infection in children remains an important problem, even in the developed world[13,14]. While the numbers of new infections have declined, in this study the majority (59%) of HIV-infected children diagnosed in Ireland were diagnosed late, (median age 10.4 years). Most children were ultimately tested for HIV, often after prolonged investigations, because of symptomatic disease or because of diagnosis in a family member. Six children (14%) were the index case in the family, and almost one fifth had progressed to AIDS at time of diagnosis. For 36% of children with late diagnosis at least one opportunity for earlier diagnosis (i.e. during a previous hospitalisation) was missed.

Failure to diagnose HIV is associated with significant risk of progressive immune compromise and associated morbidity. As optimal benefit is associated with initiation of treatment prior to the development of severe immune deficiency, such delays ultimately compromise treatment benefit.[15] Missed opportunities for diagnosis suggest either a lack of awareness among physicians of the diversity of the clinical presentation of HIV infection or a reluctance to routinely undertake HIV testing. HIV testing should no longer be the sole preserve of paediatricians with experience in HIV. Many paediatricians and general practitioners routinely test children for a variety of conditions associated with a poorer prognosis than HIV. No doubt, the reluctance to test stems from the early days of the epidemic when testing was associated with little individual patient benefit and a range of negative experiences.

This study highlights the continuing under-diagnosis of HIV infection in children and the need for a proactive approach to testing. If routine repeat HIV screening in pregnancy is not feasible, a strategy to effectively reach women at risk for seroconversion in pregnancy is needed. Given the benefits of early diagnosis and the relentless progression of disease in the absence of treatment, a more systematic approach to the screening of all children coming from high prevalence countries should be undertaken. In order to allow HIV-infected children the full benefit of ARVs HIV testing must be normalised as a routine test in general paediatric practice.

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References

1. Nourse CB, Conlon T, Hayes E, Kamiski G, Griffen G, Hillary I, Butler K. Mother-to-child transmission of human immunodeficiency virus (HIV) in Ireland: a prospective study. Ir J Med Sci. 1998 Jul-Sep;167:145-148.

2. M. Sharland, D. Gibb, G. Tudor-Williams, Walters S, Novelli V. Paediatric HIV Infection. Arch Dis Child. 1997 April;76:293â 296

3. John GC, Kreiss J. Mother-to-child transmission of human immunodeficiency virus type 1. Epidemiol Rev. 1996;18:149-57.

4. Ferguson W, Goode M, Walsh A, Gavin P, Butler K. Evaluation of 4 weeksâ neonatal antiretroviral prophylaxis as a component of a prevention of mother-to child transmission program in a resource rich setting. Pediatr Infect Dis J. 2011 May;30:408-12.

5. Centres for Disease Control and Prevention. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMW. 1994;43:1- 19.

6. Parboosing R, Naidoo A, Gordon M, Taylor M, Vella V. Resistance to antiretroviral drugs in newly diagnosed, young treatment-na ̈ flve HIV-positive pregnant women in the province of KwaZulu-Natal, South Africa. J Med Virol. 2011 Sep;83:1508-13.

7. HIV in pregnancy guidelines [Internet] Society for the Study of Sexually Transmitted Disease in Ireland [updated 2011, cited 2013 May 29th] Available from http://www.ssstdi.ie/guidelines/

8. Struik SS, Tudor-Williams G, Taylor GP, Portsmouth SD, Foster CJ, Walsh C, Hanley C, Walters S, Smith JH, Lyall H. Infant HIV infection despite â universalâ antenatal testing. Arch Dis Child 2008 Jan;93:59-61.

9. Steele RW. Late Pregnancy Screening for Human Immunodeficiency Virus. Pediatr Infect Dis J 2011 Jan;30:72-74.

10. Ferguson W, Walsh A, Cafferkey M, Butler K. Targeting Points for Further Intervention: A Review of HIV-Infected Infants Born in Ireland in the 7 Years Following Introduction of Antenatal Screening. J Int Assoc Physicians AIDS Care. 2008; 7: 182-186

11. Health Information and Quality Authority, April 2012. Economic evaluation of repeat universal antenatal screening for HIV in the third trimester of pregnancy.

12. Taylor GP, Clayden P, Dhar J, Gandhi K, Gilleece Y, Harding K, Hay P, Kennedy J, Low-Beer N, Lyall H, Palfreeman A, Tookey P, Welch S, Wilkins E, de Ruiter A.

British HIV Association guidelines for the management of HIV infection in pregnant women 2012. HIV Med. 2012 Sep;13
Suppl 2:87-157

13. Macassa E, Burgard M, Veber F Picard C, Neven B, Malhaoui N, Rouzioux C, Blanche S. Characteristics of HIV-infected children recently diagnosed in Paris. Eur J Pediatr. 2006 Oct;165(:684-7).

14. Judd A, Doerholt K, Tookey PA, Sharland M, Riordan A, Menson E, Novelli V, Lyall EG, Masters J, Tudor-Williams G, Duong T, Gibb DM. Morbidity, mortality, and response to treatment by children in the United Kingdom and Ireland with perinatally acquired HIV infection during 1996-2006: planning for teenage and adult care.Clin Infect Dis. 2007 Oct 1;45:918-24.

15. PENTA Steering Committee, Welch S, Sharland M, Lyall EG Tudor-Williams G, Niehues T, Wintergerst U, Bunupuradah T, Hainaut M, Della Negra M, Pena MJ, Amador JT, Gattinara GC, Compagnucci A, Faye A, Giaquinto C, Gibb DM, Gandhi K, Forcat S, Buckberry K, Harper L, K ̈nigs C, Patel D, Bastiaans D. PENTA 2009 guidelines for the use of antiretroviral therapy in paediatric HIV-1 infection. HIV Med. 2009 Nov;10:591-613.