



## Otorrhoea is a marker for symptomatic disease in HIV-infected children

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**Background.** Chronic otorrhoea occurs commonly in HIV-infected children. However, there are few data on incidence and severity.

**Objective.** To document the prevalence of otorrhoea in the clinic attendees.

**Methods.** A retrospective chart review was done of all HIV-I infected children seen at the Family Clinic for HIV from 1 February 1997 to 31 December 2001, a period preceding widespread availability of antiretrovirals. Otorrhoea was classified into two groups, viz. group 1 (mild): an episode lasting less than 1 month, and group 2 (severe): an episode lasting more than 1 month or more than 1 episode of otorrhoea. The clinical and immune stages of the children were noted.

**Results.** Of 326 children seen during the study period, 104

(32%) had otorrhoea. Forty-five (13.8%) had mild and 59 (18.1%) severe otorrhoea. Two hundred and eighty-eight (88.6%) had either Centers for Disease Control stage B or C disease. The median CD4 percentage in children with otorrhoea was 17.5% (8.3 - 23%) versus 21% (14 - 28%) in those without otorrhoea ( $p=0.004$ ). The odds ratio (OR) of children in stage B or C not having severe otorrhoea was 0.1 (0.01 - 0.72,  $p = 0.013$ ). The OR for immune class 2 or 3 without severe otorrhoea was 0.39 (0.18 - 0.85,  $p = 0.021$ ).

**Conclusions.** Otorrhoea contributes to the morbidity of HIV infection in children. It is a marker for symptomatic disease and CD4 depletion and should be included in clinical classifications.

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Data on suppurative complications of otitis media in HIV-infected children are scanty. A study conducted in rural KwaZulu-Natal<sup>1</sup> identified otorrhoea as a marker for HIV screening in infants presenting at primary care clinics. As we noted large numbers of children with otorrhoea presenting to the Family Clinic for HIV at our hospital, we undertook a retrospective review. Our aim was to determine the disease burden of chronic suppurative otitis media and to relate it to disease progression and CD4 depletion.

### Background

Tygerberg Academic Hospital is a tertiary facility in the Western Cape. The Family Clinic for HIV was established in January 1997. A nevirapine-based programme to reduce vertical transmission of HIV was established in our area in April 2003. Antiretroviral therapy (ART) became widely available in January 2004 through the provincial roll-out.

### Patients and methods

A retrospective chart review was done of all HIV-infected children seen at the Family Clinic for HIV from 1 February

1997 to 31 December 2001. In infants below 18 months of age, HIV infection was defined by 1 enzyme immunoassay (EIA) positive for antibodies to HIV-1, plus either P24 antigen detected with EIA, or HIV-specific RNA detected using the polymerase chain reaction (PCR). In children older than 18 months, 2 positive EIAs for HIV-specific antibodies confirmed infection.

We collected demographic and anthropometric data on all patients. Children were staged according to the 1994 Centers for Disease Control (CDC) clinical and immunological classification for HIV-infected children under the age of 13 years.<sup>2</sup> The clinical stage was noted at first presentation of otorrhoea. The CD4 T-cell percentage was recorded within a 6-month window of otorrhoea. In patients without otorrhoea, the clinical stage at first presentation and CD4 T-cell percentage within the subsequent 6 months were noted.

Otorrhoea was classified as mild (a single episode lasting less than 1 month) and severe (either a single episode lasting more than 1 month or more than 1 episode). The classification was modified from that proposed by Sabella.<sup>3</sup>

Weight-for-age z-scores (WAZs), odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using EpiInfo 2000 (CDC, Atlanta, Ga., USA). Data were analysed using JMP version 4.04 and EpiInfo 2000. Continuous data are presented as medians and interquartile ranges (IQR) and were compared using the Wilcoxon's rank test. Categorical data were compared using chi-squares. Logistical regression was performed using SAS version 9.1.3 and SAS Enterprise Guide 3.0.2. Approval to conduct this review was obtained from the institutional review board of Stellenbosch University.

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## Results

Demographic and anthropometric data are shown in Table I. Of the 326 children seen at the clinic during the study period, 104 (32%) had otorrhoea. There was equal gender distribution. The median age at which otorrhoea was first diagnosed was 21 months (IQR 13.4 - 40.4 months). Most of the children with otorrhoea had symptoms on first presentation to the clinic. Two hundred and twenty-eight children were staged to either CDC clinical class B or C. Only 15 children received ART drugs during this time, all of whom were in stage C. CD4 percentages were measured in 245 children. The median CD4 percentage in children with otorrhoea was 17.5% (8.3 - 23%) versus 21% (14 - 28%) in those without otorrhoea ( $p=0.004$ ).

Severity of otorrhoea is shown in Table II. Forty-five (13.8%) of the study population had mild and 59 (18.1%) had severe otorrhoea. Declining CD4% was related to severity of otorrhoea ( $p=0.028$ ).

In a multivariate logistical regression model, only CD4 depletion was significantly associated with 'all' otorrhoea (Wald chi-squares 6.4,  $p = 0.011$ ). Low WAZ approached significance ( $p = 0.07$ ) and stage of disease approached

significance for the absence of otorrhoea. For severe otorrhoea, no factors were significant. As the model did not fit well ( $R^2=0.066$  for presence or absence of otorrhoea and  $R^2=0.087$  for severe versus no otorrhoea), we combined clinical stages B and C for comparison with N and A (moderate or severe versus symptomatic or mild) and immunological stages 2 and 3 for comparison with stage 1 (any immunosuppression versus none) and calculated the ORs. The ORs for otorrhoea in mild or asymptomatic HIV or in the absence of CD4 depletion were significantly reduced, more so for severe otorrhoea. Data are shown in Table III. The OR for absence of severe otorrhoea was 0.1 (95% CI: 0.01 - 0.72,  $p = 0.013$ ) when stage A was compared with stages B and C.

## Discussion

We have documented that otorrhoea has a high prevalence rate in HIV-infected children without access to ART. It occurs more commonly in symptomatic than asymptomatic children and is a marker for moderate to severe CD4 T-cell depletion. The association with stage B and C disease suggests that otorrhoea might be included in a staging system for HIV-infected

**Table I. Demographic data on children attending the Family Clinic for HIV at Tygerberg Children's Hospital, February 1997 - December 2001**

	Total	Without otorrhoea (N)	With otorrhoea (N)	<i>p</i> -value
Total	326	222 (68%)	104 (32%)	
Male/female ratio		103:115	55:51	0.19
Age* (mo.) (median)		16.7 (IQR 7.4 - 45.4)	19.4 (IQR 10.6 - 35.7)	0.93
Weight-for-age z-score (median)		-1.83 (IQR -2.7 - -0.7)	-2.16 (IQR -3.2 - -0.9)	0.24
CDC classification				
N	5 (2%)	5 (3%)	0	0.14
A	33 (10%)	27 (12%)	6 (5%)	
B	172 (53%)	112 (50)	60 (57%)	
C	116 (36%)	78 (35%)	38 (37%)	
CD4% <sup>†</sup> (median)		21 (IQR 14 - 28)	17.5 (IQR 8.25 - 23)	0.004

\*Age in months at first episode of otorrhoea, or age at first visit without otorrhoea.

<sup>†</sup>CD4 percentages measured in 245 children.

**Table II. Severity of otorrhoea and the Centers for Disease Control (CDC) clinical and immunological classification of HIV-infected children (N (%))**

	Mild otorrhoea (<4 wks duration)	Severe otorrhoea* (>4 wks duration and/ or >1 episode)	Otorrhoea absent	<i>p</i> -value
Clinical classification	N=45 (13.8%)	N=59 (18.1%)	N=222 (68%)	
N	0	0	5 (2%)	0.054
A	5 (11%)	1 (2%)	27 (12%)	
B	27 (60%)	33 (56%)	112 (50%)	
C	13 (29%)	25 (42%)	78 (35%)	
CD4% <sup>†</sup> (median)	21% (IQR 14 - 27%)	18% (IQR 8 - 30%)	16% (IQR 7 - 22%)	0.028

\*Severe otorrhoea >4 weeks - 21 and >1 episode - 38.

<sup>†</sup>CD4 percentages measured in 245 children.



Table III. Odds ratios for severity of otorrhoea and severity of HIV disease

	Disease classification	Odds ratio (OR)	95% CI	p-value*
Otorrhoea				
Severe	N + A v. B + C	0.10	0.01 - 0.72	0.01
	B v. C	0.92	0.49 - 1.74	0.90
All	N + A v. B + C	0.36	0.13 - 0.95	0.037
	B v. C	1.1	0.65 - 1.87	0.80
Immunological classification				
Severe	I v. II + III	0.39	0.17 - 0.88	0.02
	I v. II	0.39	0.15 - 0.98	0.04
	II v. III	0.98	0.44 - 2.18	0.89
All	I v. II + III	0.64	0.34 - 1.19	0.17
	I v. II	0.70	0.34 - 1.45	0.39
	II v. III	0.82	0.40 - 1.68	0.69

\*Yates's corrected chi-square test.

children. The association with at least moderate CD4 depletion suggests that it may be an especially useful marker where lymphocyte subsets cannot be measured.

To the best of our knowledge, this study is one of only two comprehensive surveys done on otorrhoea in HIV-infected children. In other studies, otorrhoea was noted but neither incidence data nor relationship with severity of HIV disease in children were explored. Otorrhoea occurred in 14 (19.4%) of 72 children from Great Ormond Street Hospital in the UK.<sup>4</sup> All children showed at least moderate immunosuppression. In a study from KwaZulu-Natal evaluating markers for HIV testing in primary care clinics, the odds of a child with otorrhoea being HIV-infected were 3.2.<sup>1</sup> Lastly, in a survey of 391 Ethiopian children with chronic suppurative otorrhoea, HIV infection was reported to occur commonly.<sup>5</sup>

In a review of otitis media in developing countries, Berman noted that the prevalence of otorrhoea varied between 0.6% and 4.4% of children attending schools.<sup>6</sup> In a recent survey of children aged 2 - 5 years in South India, the prevalence was 5.7%.<sup>7</sup> The associated hearing loss causes significant morbidity.<sup>5,7</sup>

As this was a retrospective study, we were unable to comment on response to antiretroviral therapy or document causative organisms. Schaaf *et al.* had previously cultured *Mycobacterium tuberculosis* from children with chronic otorrhoea.<sup>8</sup> Also we could not comment on morbidity or management of otorrhoea.

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## Conclusions

Severe otorrhoea should be included as a criterion for moderate to severe disease and as a marker for CD4 depletion. Otorrhoea

is a significant burden in HIV-infected children. Otitis media should be managed aggressively to prevent suppurative complications.

Paediatric staff attending to children with HIV infection should be familiar with management of otological complications of the disease and otorrhoea. Hearing should be assessed in all these cases, as hearing loss will impact significantly on the language development and school performance of these children.

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