ORIGINAL ARTICLE

Nocturnal enuresis is a common complication following cardiac transplantation

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Aims: To investigate the incidence of nocturnal enuresis post-cardiac transplantation.
Methods: Seventy two cardiac transplantations have been performed in children under 16 years of age. All recipients who were alive and over 4 years of age at the time of the study received a questionnaire about urinary symptoms; 54 of the 57 eligible children participated.
Results: Twenty five children had persistent nocturnal enuresis post-transplantation. Thirteen of them had previously attained reliable night-time dryness but developed secondary nocturnal enuresis following transplantation, with three subsequently regaining dryness at ages 8, 12, and 17 years; 10 were still wetting mean age 12.3. Twelve children had not achieved night-time dryness when transplanted (all were under 4 years of age at the time) and continued to wet. Only one of these children achieved dryness (at age 12 using oxybutynin); the other 11 remained wet at night at a mean age of 9.3 years. Twenty nine children were dry at night post-transplantation, but 21 of them had nocturia at least three times a week. There is a significant difference in age at transplantation between the primary nocturnal enuretic children (mean age 2.0) and the secondary nocturnal enuretic children (mean age 7.4) as well as between the primary nocturnal enuretic children and the non-enuretic children (mean age 9.0).
Conclusions: Transplanting young children frequently delays the normal attainment of night-time continence or causes them to start wetting again. It should not be dismissed as a minor problem as it causes low self-esteem and is socially limiting. It is important families are aware it is a direct result of the transplantation process.

Many complications of paediatric cardiac transplantation are well recognised. These include rejection, post-transplantation coronary disease, and side effects of immunosuppressive drugs such as infection, post-transplantation lymphoproliferative disease, renal impairment, and hirsuitism.[1 2]

We report primary and secondary nocturnal enuresis as common complications following paediatric cardiac transplantation. They have not previously been described.

METHODS

Patient population

We transplanted 72 children under 16 years of age between the start of our cardiac transplantation programme in October 1985 and 1999. There were 11 deaths prior to the start of this study. Four children were excluded as they were under 4 years of age at the time of study and would not be expected to have attained nocturnal continence. Fifty four of the remaining 57 children participated in the study.

Children were treated with a maintenance immunosuppressive regimen of cyclosporin and azathioprine, which has been described in detail elsewhere.[3]

No children had significant neurodevelopmental delay (all were at mainstream school in age appropriate year). No children were taking maintenance diuretics, although most were treated with diuretics in the first month post-transplantation. Urinary infection was excluded by urinalysis (dipstick and microscopy if dipstick was positive).

Data collection

A questionnaire was sent to parents of all children eligible for the study. Definitions of nocturnal enuresis vary. We used a popular definition of children who had involuntary voiding of urine on at least one night a week.[4]

Statistics

An unpaired *t* test was used to compare age at transplantation of the primary enuretic, secondary enuretic, and non-enuretic children.

RESULTS

Primary nocturnal enuretics

Twelve children were not dry at night at time of transplantation; their mean age at transplantation was 2.0 years (range 0.2–3.9). Only one child had attained night-time dryness following transplantation at age 12 years. The other 11 remain wet at night at a mean age of 9.3 years (range 4.7–12.8). Only two of them are still less than 7 years old.

Secondary nocturnal enuretics

Thirteen children were reliably dry when transplanted and subsequently restarted wetting. All children who restarted wetting did so within a month of transplantation. Their mean age at transplantation was 7.3 years (range 2.3–14.1). Three children have regained night-time continence at ages 8, 12, and 17 respectively, but the other 10 remain enuretic with a mean age of 12.3 years (range 4–19.6). Only one of them is less than 7 years old.

Non-enuretics

Twenty nine of the 54 children in the study had not experienced problems with enuresis. Their mean age at transplantation was 9.0 years (range 0.4–15.6).

There is a statistically significant difference ($p<0.001$) in age at transplantation between the primary nocturnal enuretic children and the secondary nocturnal enuretic children, as well as between the primary nocturnal enuretic children and the non-enuretic children ($p<0.001$). There was no statistically significant difference in age at transplantation

between the secondary nocturnal enuretic and non-enuretic children.

Frequency of enuresis
Of the 21 children currently wetting, 13 children had nocturnal enuresis every night, two at least three times a week, and six once or twice a week.

Nocturia
Twenty nine children had not experienced problems with enuresis. However, 27 of these children had nocturia, with 21 waking to void at least three times a week. There is a statistically significant difference ($p<0.001$) in age at transplantation between the primary nocturnal enuretic children and the children with nocturia, but not between the secondary nocturnal enuretic children and the children with nocturia.

Family history
Three children (all primary nocturnal enuretics) had a family history of nocturnal enuresis in parents or siblings. None of the others reported a positive history in any family members.

Associated symptoms
Two girls (one primary enuretic and one non-enuretic) reported daytime urgency, but no child had a problem with daytime enuresis. One child had a history of soiling, although they were not enuretic.

Diagnosis at transplantation
Thirty three children were transplanted because of cardiomyopathy, and 21 with congenital heart disease (table 1).

DISCUSSION
The incidence of nocturnal enuresis in otherwise healthy children has been reported as 15% at 5 years of age with a spontaneous resolution frequency of 15% a year.[5] By age 7, around 90% of well children are dry at night.[6 7] Our study reveals a high incidence of nocturnal enuresis post-cardiac transplantation, with 46% (25/54) of children in the study being wet at night. Only 16% (4/25) of the nocturnal enuretics have subsequently become dry, and this has been achieved late at 8, 12 (2), and 17 years of age. The remaining 21 children still have a problem with bedwetting well beyond an age when they would be expected to be dry at night (only three are presently under 7 years of age).

The reasons for the high incidence in the study group are uncertain, particularly as the pathophysiology of nocturnal enuresis in otherwise healthy children is complex. There is often a strong family history and genetic component.[8–10] This does not appear to be the case with the post-transplantation nocturnal enuretics and other mechanisms must be responsible.

A tendency to nocturnal polyuria[11 12] and poor urine concentrating ability[13] has been noted in nocturnal enuretics. Nocturnal enuretics tend to have higher urine production on wet nights.[14] This may be due to disturbances of the normal diurnal variation in vasopressin[6 15 16] or atrial natriuretic peptide levels.[17] Enuretics also are reported to have a reduced functional bladder capacity compared to healthy controls.[18] Functional bladder capacity increases steadily with age and it is thought that enuresis occurs when the high volume of night-time urine production exceeds the functional bladder capacity.[5]

Cardiac transplantation recipients have abnormal cardiac and renal neuroendocrine reflexes,[19] partly because the transplanted heart is denervated and partly because of the side effects of cyclosporin mediated via the autonomic nervous system.[20] The majority of transplant recipients are hypertensive, often with the loss of diurnal variation in blood pressure.[21 22] Differences in the release of vasopressin,[23] hypersecretion of atrial natriuretic peptide,[19 24] and loss of the usual patterns of diurnal variation of atrial natriuretic peptide, rennin, and aldosterone[25–27] have also been noted in cardiac transplant recipients.

It is likely that following cardiac transplantation there is loss of the normal diurnal variation in urine production. The resultant nocturnal polyuria causes nocturia in older children and adults and enuresis in younger children when functional bladder capacity is suddenly exceeded. A parallel situation has been described in newly diagnosed diabetics who start to wet the bed concomitantly with the development of polyuria.[28]

Impaired renal function is common post-cardiac transplantation but is unlikely to contribute to the pathophysiology of nocturnal enuresis in this group, as the temporal association is wrong. The children with secondary enuresis restarted wetting within the first month post-transplantation. During this period renal function is well preserved and often better than pre-transplantation.[29–31] Nocturnal enuresis is not a feature of impaired renal function in other circumstances; as overall renal function declines the volume of urine produced falls.

It is surprising that such a common complication has not been reported before. This may be because families think it is too trivial to inform the doctor about in comparison to their child's other medical problems. There may be embarrassment, especially with older children, so the information is not volunteered. People caring for paediatric cardiac transplant recipients should ask specifically about nocturnal enuresis and discuss this complication during pre-transplantation counselling. It is very important to inform the family that nocturnal enuresis is a direct result of the transplantation process to avoid the child being ''blamed'' for the wetting. They should also be reassured that nocturnal enuresis is not due to psychological problems.[10 32 33] Although it may not be regarded as a serious or life threatening medical problem, the impact on children and their families must not be underestimated. For the child, it adds to low self esteem, is socially limiting, can aggravate skin problems caused by cyclosporin, and reinforces that a child with a transplant is different from their peers. Nocturnal enuresis also has economic and social implications for the rest of the family,[34] adding to the burden of looking after a child with a cardiac transplant.

Table 1 Diagnosis at transplantation

	Cardiomyopathy	Congenital heart disease
Non-enuretic	22	7
Primary nocturnal enuretic	6	6
Secondary nocturnal enuretic	5	8
Total	33	21

APPENDIX 1: SUMMARY OF QUESTIONNAIRE
Current age: …years …months

Do you get up at night to go to the toilet?

- more than once a night
- every night
- almost every night
- 3 times a week or more
- 1–2 times a week
- less often

Do you wet the bed? Yes/No
How often?

- every night
- almost every night
- 3 times a week or more
- 1–2 times a week
- once every couple of weeks
- once a month
- less often

Age when dry (out of nappies)

- During the day: …years …months OR …not dry
- At night: …years …months OR …not dry

If you were dry at night before the transplantation, did you start wetting the bed again afterwards? Yes/No

How old were you when you stopped again? …years …months

Bedwetting sometimes runs in families. Did anyone else in your family have problems with bedwetting?

- Yes – brothers or sisters
- Yes – parents
- No

If you tried any treatments for bedwetting:

- What was it called?
- Did it help ?
  - No
  - Helped a little
  - Helped a lot

Any comments?

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