Dilated Cardiomyopathy in the Scottish Paediatric Population: Aetiology and Outcomes

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What is already known on this topic?

- Paediatric dilated cardiomyopathy (DCM) is the commonest of the childhood cardiomyopathies, with significant associated morbidity and mortality.
- DCM is most commonly idiopathic.
- DCM secondary to vitamin D deficiency is rare but readily treatable and reversible.

What this study adds?

- Identifying the aetiology of DCM in the paediatric population aids risk stratification and prognostication.
- Regardless of aetiology, the first year after diagnosis of DCM is associated with significant mortality.
- Males are significantly less likely to survive to one year post diagnosis.
- The survival from DCM in the paediatric population in Scotland has improved in the modern era.

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Abstract

Background

Dilated cardiomyopathy (DCM) is the most common form of the childhood cardiomyopathies and is known to result in significant morbidity and mortality in the paediatric population [1,2].

Objective

To review the aetiology and associated outcomes of DCM in Scottish children.

Methods

A retrospective data review of 43 consecutive cases of DCM diagnosed in a national paediatric cardiology centre from 1st September 2000 - 1st September 2015. All paper and electronic case notes were reviewed to identify the aetiology; age at presentation; need for intensive care i.e. mechanical ventilation; inotropic support; extra-corporeal life support (ECLS); cardiac transplantation; and to report the longer term outcomes.

Results

43 patients were diagnosed with DCM during the study period. The median age at diagnosis was 10 months (range = 0-42months); 28 (65%) cases were diagnosed within the first year of life and 42 (98%) cases were diagnosed before the child's second birthday. 25 cases were female, 18 were male; with a male: female ratio of 1:1.4. In the cohort 82% were Caucasian; 9% Black and 9% of Asian ethnicity. Over half the cases (51%) were idiopathic; 23% secondary to a viral infection; 16% metabolic or genetic disorders and 10% as a result of vitamin D deficiency. Parvovirus B19 was the most common infectious agent identified in 60% of cases, with an additional 30% secondary to enteroviruses. 60% of the children required inotropic support and extra corporeal life support was administered in 19% of cases. Six of the

18 (30%) males died; one MYH7 gene positive; one long chain fatty oxidation disorder; one viral and three idiopathic DCM. Only one (4%) of the 25 females did not survive, and males were significantly less likely to survive to one year of age $p = 0.015$. The median age at diagnosis did not alter survival to one year and the estimated survival proportion in the cohort beyond one year was 83.7% (95% CI, 71.3 to 94.5%), with all deaths occurring within one year of presentation.

Conclusion

Paediatric dilated cardiomyopathy is a heterogeneous disease resulting in significant morbidity. In the paediatric population the aetiology alters the age at presentation and identification is also a useful tool for risk stratification and prognostication. DCM is idiopathic in around 50% of cases. The first year after diagnosis is a critical time reflected in significant morbidity and mortality.

Introduction

Dilated cardiomyopathy (DCM) is the most common form of cardiomyopathy in children[3]; defined by the World Health Organization as a disorder 'characterized by dilation and impaired contraction of the left ventricle or both ventricles' in the presence of normal wall thickness [1,2]. The onset of the disease may be subtle and insidious, or alternatively acute and life threatening. At initial presentation DCM may be mistakenly diagnosed as an isolated respiratory tract infection or viral illness, and not initially considered a differential diagnosis unless cardiomegaly is detected on a chest x-ray; failure to respond to conventional supportive management or profound cardiovascular collapse. Despite advances in the diagnosis and medical management of paediatric DCM, the morbidity, mortality and impact on hospital admissions remains significant[4]. The aim of our study was to review the aetiology of dilated cardiomyopathy and the associated outcomes in the Scottish paediatric population.

Methods

A retrospective data review of 43 consecutive cases of DCM, aged <18 years, diagnosed in the Scottish national paediatric cardiology centre from the 1st September 2000 - 1st September 2015. The departmental database Heartsuite (Heartsuite, Systeria, Glasgow, UK) was used to identify patients and provide initial patient data. In addition, electronic and paper case notes were reviewed to identify the age at presentation; aetiology, need for intensive care support; mechanical ventilation; inotropic support; extra-corporeal life support (ECLS); cardiac transplantation and the associated long term mortality. In order to determine potential links between deprivation and the incidence of DCM, the Scottish Index of Multiple Deprivation (SIMD) was utilized. SIMD is a tool employed by the Scottish Government to identify areas of multiple deprivation in Scotland. The index scores Scottish regions from one to five, where five indicates the lowest level of deprivation.

Patients with structural heart disease, cardiomyopathy secondary to sustained arrhythmias; coronary artery disease, or anthracycline toxicity were excluded from the study. Diagnosis was based upon clinical features of heart failure and echocardiographic evidence of global systolic dysfunction; left ventricular diastolic dimensional Z score of more than two standard deviations above normal, and a fractional shortening (FS) less than 25%. Global speckle strain imaging is currently used in our centre to monitor systolic function, however this modality was not utilised routinely in the early cohort. Transthoracic echocardiography was used as a diagnostic tool and to monitor disease progression. Measurements of left ventricular cavity and wall-thickness at end diastole, end systole, as well as estimation of fractional shortening and ejection fraction were documented in all cases. Resolution of DCM was defined in the absence of clinical features of heart failure; normal cardiac function and normal left ventricular dimensions reported by transthoracic echocardiography.

As the study sample was small, statistical significance tests i.e. Mann-Whitney test, Pearson Chi-Square test and Fisher's exact test were employed in the analysis of contingency tables. These logistic tests were used to evaluate the significance of aetiologies, age at presentation, gender, ethnicity, deprivation, season at presentation, inotrope usage, invasive mechanical ventilation, extra corporeal life support (ECLS) and heart transplant related to outcomes.

Results

43 consecutive patients were diagnosed with DCM during the study period; the demographics are illustrated in Table 1. The median age at diagnosis was 10 months (range 0-42 months) with 28 (65%) patients diagnosed within the first year of life and 42 (98%) cases diagnosed in children before their second birthday (Figure 1). DCM was more common among girls, 25 (58%) cases of DCM compared to 18 (42%) in the male population. Male: female ratio 1:1.4. Survival to one year after the initial diagnosis was significantly lower in the male population

(p=0.015) as only one (4%) female in the cohort did not survive. In the cohort, 82% were Caucasian; 9% Black and 9% of Asian ethnicity. The median SIMD score was three and further analysis did not demonstrate a significant association between the SIMD and incidence or mortality associated with DCM.

Presenting Features

The presenting clinical features varied in severity: 60% (n=26) had overt signs of heart failure - three patients presenting with heart failure had severe cardiovascular compromise requiring paediatric intensive care admission; 14% (n=6) had isolated respiratory symptoms at presentation; 14% (n=6) presented with failure to thrive and feeding difficulties. Other presenting signs or symptoms included: supraventricular tachycardia 2% (n=1); heart murmur 2% (n=1) and seizures 2% (n=1). Two (4%) asymptomatic patients with a family history of DCM were detected routinely during familial screening.

Aetiology

51% of DCM cases were classified as idiopathic, therefore no cause was identified. In several cases the children presented with signs and symptoms of a viral illness, but despite extensive virology work up no viruses were isolated. Endomyocardial biopsy was not routinely undertaken in our patients. A viral aetiology was the most common identifiable cause of DCM, evident in 23% of cases: 60% of which were secondary to Parvovirus B19; and 30% due to enteroviruses (Figure 2). There was evidence of seasonal variation, with an increased incidence of DCM diagnosis in autumn n=18, (42%) (Figure 3,4). 16% (n=7) of DCM cases were as a consequence of a metabolic or genetic abnormality: MYH7 gene mutation n=3; Barth's syndrome n=1; combination of Barth's syndrome and MYH7 gene mutation n=1; long chain CoA dehydrogenase deficiency n=1, I-cell disease (MPS type II) n=1. Within the metabolic and genetic cohort, the male to female ratio was higher 6:1 in comparison to the total population, male: female 1:1.4. Due to the small sample size the Chi-square test was not

significant. Vitamin D deficiency was reported in 10% (n=4) of DCM cases, with a median age at diagnosis of 4.5 months compared to 10 months in the full cohort (Figure 1); three children were of Asian or Black descent and only one was Caucasian. All cases of vitamin D deficient DCM patients achieved full recovery after receiving appropriate supplementation, including one child requiring ECLS as a bridge to recovery.

N=26 (60%) of the DCM population required inotropic support, n=19 (44%) required mechanical ventilation and N=8 (19%) required ECLS as a bridge to recovery or cardiac transplant, of which six patients survived and made a full clinical and echocardiographic recovery. Transplantation is routinely discussed with families in the presence of escalating intensive care support and cardiovascular instability. In our population, 18 families (42%) consented to transplant referral. Of the patients discussed, n=7 were placed on the non-active transplant list, and all were subsequently removed from the list after resolution of the DCM. In contrast, a total of 11 were accepted onto the active transplant list: n=4 restored normal cardiac function and were subsequently removed from the list; n=4 died awaiting transplant and n=3 were successfully transplanted and all are alive to date (Figure 5).

Unfortunately, our sample size was too small for formal statistical analysis to suggest such association between aetiology and survival.

Mortality

The reported survival from initial diagnosis to one year post diagnosis was 83.7% (95% CI, 71.3 to 94.5%), the median age at diagnosis did not alter survival to one year and observationally more deaths occurred in the winter months but the sample size was too small for formal statistical analysis. Males were more likely to have DCM secondary to a genetic and metabolic disorders (P-Value = 0.020) and were statistically less likely to survive one year from diagnosis (P-Value = 0.015). Six (30%) males died within the first year of diagnosis; one MYH7 gene positive, one long chain fatty oxidation disorder, one of viral aetiology and three

idiopathic DCM. In contrast only one (4%) female died within the first year of diagnosis secondary to idiopathic DCM. Children requiring ECLS were less likely to survive, but this did not reach statistical significance at the 95% CI level (P-Value = 0.106) due to the smaller sample size.

Discussion

Dilated cardiomyopathy is a heterogeneous disease with reported prevalence in the paediatric population ranging from 1 in 140 000 in Australia to 1 in 170 000 in the US[5]. Some milder cases of dilatation may be detected during familial screening for DCM as in our cohort, however the majority of children with DCM are symptomatic at presentation. In the future, wider use of genetic testing may identify asymptomatic carriers of DCM in the paediatric population. Recent advances have been made in the understanding of the genetic aetiology of DCM. Hershberger et al identified more than 30 genes of various ontologies which are thought to contribute to approximately 40- 50% of the genetic causes of DCM[6,7].

Despite these advances a significant proportion of paediatric DCM cases remain classified as idiopathic, in some studies as many as 66% of reported cases[8]. Our study confirms that a significant proportion of DCM in the paediatric population is idiopathic despite comprehensive metabolic, genetic investigations and viral PCRs. An endomyocardial biopsy is not a first line investigation for DCM within our cardiac centre, thus in some cases a viral aetiology may not have been identified. Identifying an aetiology, where possible, is a useful tool for clinicians to provide risk stratification and prognostication for families. This is particular true in the rarer cause of dilated cardiomyopathy, secondary to vitamin D deficiency. Vitamin D is a steroid hormone which binds nuclear receptors in the heart altering gene transcription[9]. Exposure of ultraviolet radiation on the skin is a crucial source of vitamin D and ethnic groups with darker skin in the UK are at greater risk, particularly between October to the beginning of April[10]. A

retrospective review by Maiya et al identified 16 paediatric patients with DCM secondary to vitamin D deficiency over a 6-year period in the South East of England[11]. All patients were of non-Caucasian ethnicity. Our study confirms that vitamin D deficiency cardiomyopathy is reversible with prompt identification and supplementation, in addition the use of ECLS is strongly indicated as a bridge to recovery in this cohort[12]. The role of vitamin D and cardiac function is an area of increasing study, demonstrated by the VINDICATE (VitamIN D treatIng patients with Chronic heArT failurE) trial in the adult population with chronic heart failure. Witte et al demonstrated that administering high dose vitamin D in addition to optimal medical heart failure therapy increased left ventricular ejection fraction by 8%[13].

In spite of optimal medical management, our study confirms the first year of life is a critical period for outcome and other studies concur that a significant proportion of children will be re-hospitalized and/or require cardiac transplantation within one year of presentation[14,15]. Puggia et al demonstrated an 82% survival at one year; 71% and 68% survival at six and nine years respectively. Their data also suggested that idiopathic DCM in the paediatric population has a poorer prognosis than the adult DCM population, even when the baseline left ventricular function was higher[5]. An Australian study by Daubenay et al reported freedom from death or transplantation at one and five years respectively; 72% and 63%. Risk factors for a poorer outcome included: familial dilated cardiomyopathy; age > 5 years at diagnosis and a lower fractional shortening at presentation[16].

An earlier study from our institution examining the outcome of DCM in the paediatric population of Scotland between 1980 and 1997 also reported all deaths occuring within the first year of life. Survival at one year and nine years was 69%[17]. Our recent study demonstrates that mortality in this cohort remains significant, but has improved in the modern era, 2000-2015, with survival to one year 83.7%, and no cardiac deaths after one year in the current follow

up. This may reflect continual improvements in the medical management of heart failure, advances in intensive care support and the provision of ECLS in our cardiac centre.

Bharucha et al reported the risk of sudden cardiac death (SCD) in the DCM population at 5% (95% CI: 2% to 11%) after 15 years of follow up and increased risk if familial DCM, older age at diagnosis and lower fractional shortening at diagnosis [18]. This study found no evidence of SCD once the left ventricular function had normalised. In addition, Dimas et al demonstrated a 1% risk of SCD in the paediatric idiopathic DCM population, in contrast to the adult DCM population ranging from 20-75%[19]. In the paediatric population with severe DCM, cardiac transplantation is the final recourse in the management of terminal heart failure[14], with DCM continuing to be the most common indication for heart transplantation in children over the age of five [2].

Limitations

This cohort included all cases of dilated cardiomyopathy referred to a national centre however the study was retrospective and the sample size was small, therefore some data did not reach statistical significance.

Conclusion

Paediatric dilated cardiomyopathy is a heterogeneous disease, with an unidentified aetiology in around 50% of cases, resulting in significant morbidity. In the paediatric population the aetiology alters the age at presentation and identification is also a useful tool for risk stratification and prognostication. The first year after a diagnosis of DCM is a critical time reflected in significant morbidity and mortality.

Author contributions

All the authors contributed substantially to researching and writing this manuscript, and to reviewing/editing it before submission.

Competing interest statement

The authors declare no competing interests.

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Demographics	No. (%)
Patients	43
• Female	25 (58%)
• Male	18 (42%)
Ethnicity	
• Caucasian	35 (82%)
• Black	4 (9%)
• Asian	4 (9%)
Aetiology	
• Idiopathic	22 (51.20%)
• Viral	10 (23.30%)
• Metabolic/Genetic	7 (16.30%)
• Vitamin D Deficiency	4 (9.30%)
Median age at diagnosis	10 mon; range= 0-42
• Metabolic/Genetic	4 mon; range= 0-14
• Vitamin D Deficiency	4.5 mon; range= 1-8
• Viral	15 mon; range= 1-23
• Idiopathic	11mon; range= 2-42
Echocardiographic Features	
• Fractional shortening (mean)	11.5%
• Ejection Fraction (mean)	29.1%
• LVDED	42 mm
Outcome	
• Transplant Referral	18 (41.90%)
• Heart Transplantation	3 (7%)
• Mortality	7 (16.3%)
• Survival at 1 year	36 (83.7%)

Table.1 Patient Demographics

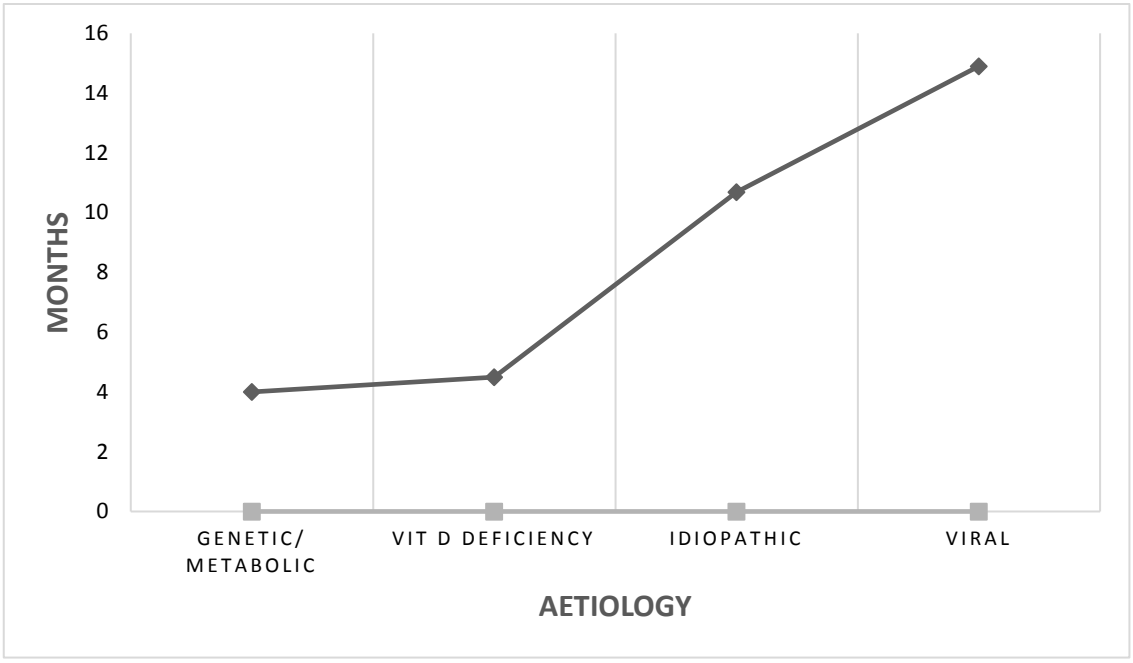

Figure 1 Median Age at Presentation

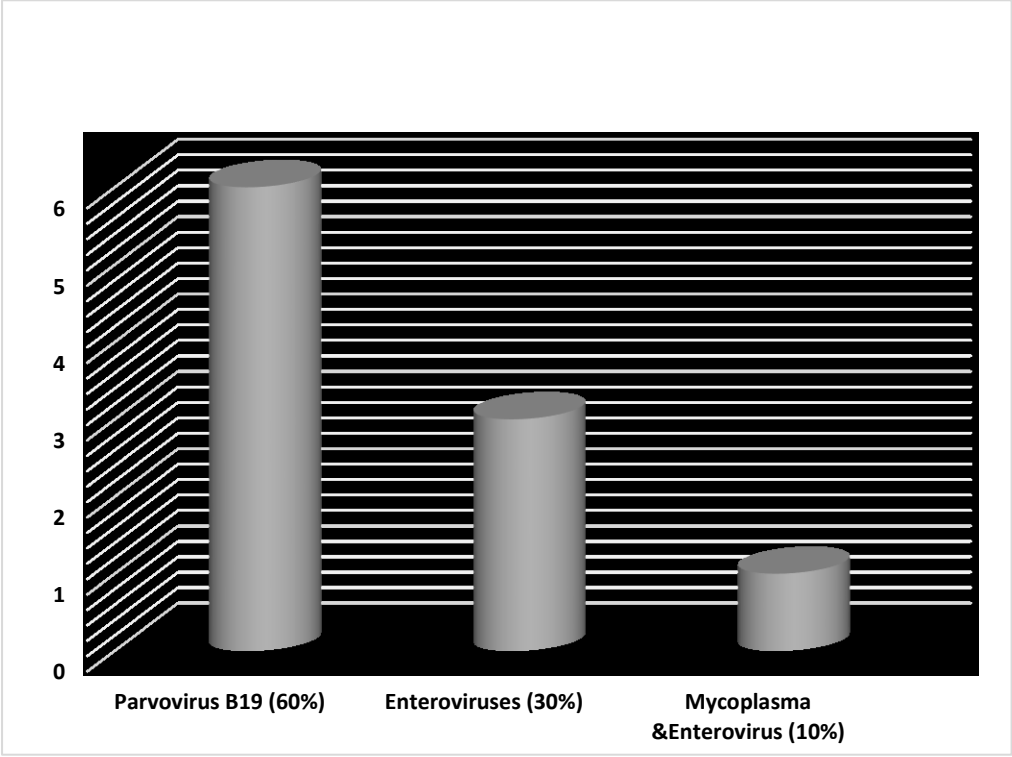

Figure 2 Viral Aetiology

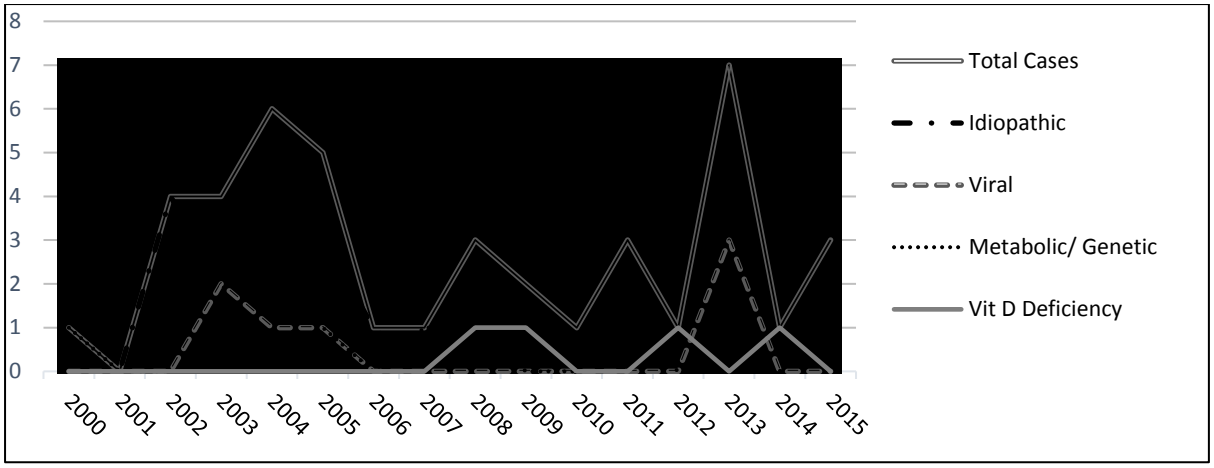

Figure 3 Annual incidence of DCM.

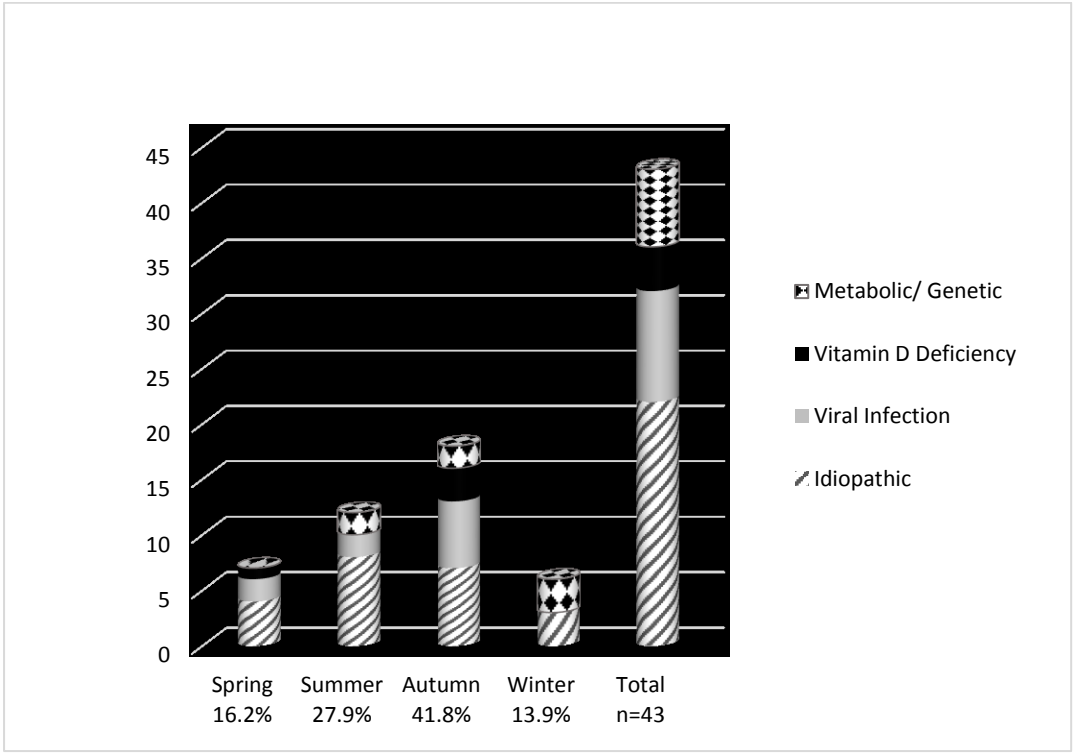

Figure 4 Seasonal Variation in Aetiology

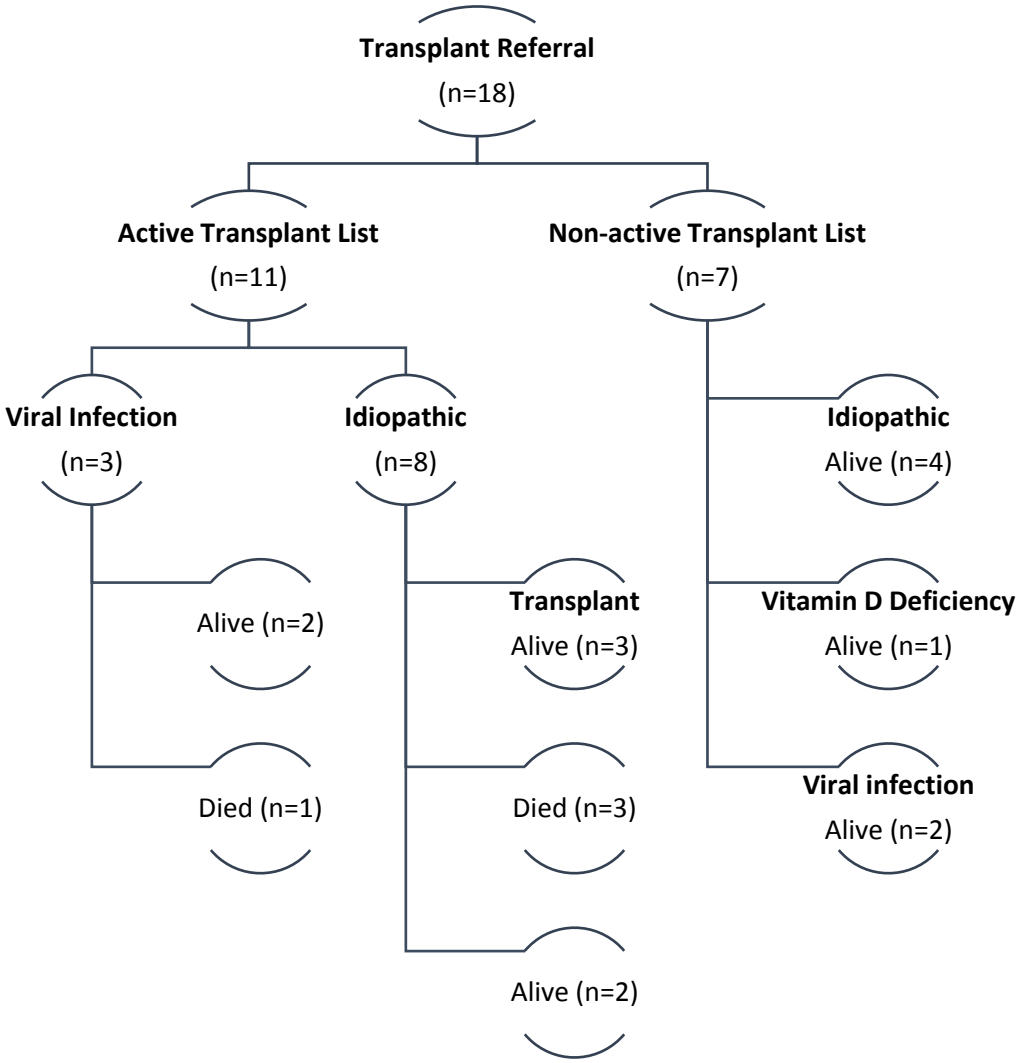

Figure 5 Outcome after Referral for Transplant.