5. Figure 5: there are some inconsistencies in recording the death of affected case III-10.

6. Phenotype D (on page 191): “In all 20 patients, either atrial fibrillation (n = 14) or AV block (n = 7) was documented...” Again the numbers do not add up correctly. Should the text read ‘atrial fibrillation and/or AV block’?

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References

Reply

We thank Dr. McKeown for his supportive and critical comments concerning our recently published manuscript. Our paper summarizes a 5-year effort to elucidate the frequency and clinical phenotypes of familial disease in 445 index patients with invasively documented dilated cardiomyopathy (DCM). We could show that familial aggregation of the disease is possibly present in 35% of all index patients. These findings indicate the need for a careful history taking in patients with DCM. As with any work that attempts to analyze the families of 445 index patients some important points cannot be addressed in a depth due to limitations in time and manpower.

Thus, we agree that in 58 cases familial disease could not be excluded definitely since we were not able to investigate the family members for presence of dilated cardiomyopathy by clinical examination, ECG-recording, and cardiac ultrasound. Thus, indeed it may be possible that the prevalence of familial disease may have been even higher than reported. However, we have commented on this limitation and thus had hoped that this limitation is apparent to the reader.

We also agree, that the definition of suspected DCM is rather loose. However we felt: a) that the wording of “suspected” implies a residual uncertainty, and b) that the diagnosis suspected DCM is still a valid information, considering the difficulties of proper clinical classification of the presence of absence of DCM.

Our intention was to emphasize that patients with familial DCM may represent with different phenotypes, which are important for diagnostic classification and for further risk stratification of the patients and may be helpful for genetic analysis. The issue of potential autosomal recessive disease was not explicitly addressed because an autosomal recessive way of inheritance was not certainly observed in our study and may indeed be very rare (2,3).

Table 1 summarizes the clinical definitions of phenotypes and their possible genetic causes, whereas table 3 and 4 classify clinical findings of the examined families. We agree that a more uniform presentation may have facilitated the reading of the tables.

The major clinical difference between group A and B was that of an elevation of creatine kinase activity in serum in group A patients. The elevation of CK activity in blood was taken as evidence for the involvement of skeletal muscle disease, which is a common finding in patients with mutations of the dystrophin molecule. Indeed, we were able to identify a dystrophic mutation in one of the two families. This certainly is no proof that all cases of CK positive DCM may be caused by dystrophin mutations. However, it is likely that dystrophin mutations may also have been present in the second family.

We furthermore appreciate the detailed correction of typographical errors, although they do not pertain to any of the results or any of the conclusions made in this study: Figure 1 n = 108 instead of 110 and Figure 5 III-10 instead of III-10. On page 191, “and/or” may indeed be better than “or.” It is correct, that patient IV12 in Figure 2 should read as cousin and not as nephew. Finally, it was not possible to give a functional status in individuals diagnosed as DCM by autopsy, leading to the erroneous conclusion of “missing data” in Table 3.

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