“How Sick Must Your Mouse Be?” — An Analysis of the Use of Animal Models in Huntington’s Disease Research

Nuno H. Franco and I. Anna S. Olsson

IBMC — Institute for Molecular and Cell Biology (Laboratory Animal Science Group), University of Porto, Porto, Portugal

Summary — Refinement measures to improve animal welfare can ease the ethical dilemma between human benefit and animal harm in research with animal models of neurodegenerative diseases. To evaluate the potential for refinement, as well as its implementation in research, we analysed papers on murine models of Huntington’s disease (HD) published between 1999 and 2009 (n = 233). Each study was classified according to a four-level severity scale, in terms of the disease stage that animals were allowed to reach, the execution of invasive procedures, and the implementation of refinement. Reports of ethical approval, and regulatory compliance in general, followed a clear rising trend over the years reviewed (p < 0.001). However, the proportion of high-severity studies did not change over that period. Also, of the studies for which approval was reported (n = 120), 36% were attributed the highest severity level. The observed discrepancy between the rising motivation to affirm regulatory compliance, and the unaltered proportion of studies allowing animals to reach severely distressful stages, raises both ethical and methodological issues, which we discuss in this paper.

Key words: animal models, animal welfare, bioethical issues, Huntington’s disease, neurodegenerative diseases.

Address for correspondence: Nuno Franco, IBMC, Rua do Campo Alegre, 823, 4150-180 Porto, Portugal.
Email: nfranco@ibmc.up.pt

Introduction

The use of animal models has been important for the understanding of the underlying genetic and pathophysiological mechanisms of hereditary neurodegenerative diseases, such as Huntington’s disease (HD), especially since the development of genetically modified (GM) mice expressing phenotypic traits that resemble some of the most relevant symptoms observed in human HD patients (1–5). While this progressively debilitating disorder — which ultimately culminates in early death — causes great human suffering (6, 7), its toll on animal wellbeing is also worthy of ethical concern (8).

Each type of model presents its own particular advantages and disadvantages from scientific (3, 9, 10) and animal welfare points of view. With regard to animal welfare, transgenic models expressing an N-terminal fragment of the mutant huntingtin gene (HTT; such as the R6/2) present the most challenging issues, because of the early onset of pathology and rapid disease progression (for an overview of the most common murine models of HD, see Table 1). Full-length mutant HTT models, in comparison, present a slower and later-onset progressive phenotype, and have a longer survival time. As for knock-in models, these usually show much milder and later-onset clinical signs than both types of transgenic models, and have a normal lifespan (10–12).

The ethical appraisal and approval of experimental protocols requiring the use of animals is seen as a means of ensuring that such experiments are ethically justified (13, 14) — i.e. that the ‘cost’ (the suffering endured by laboratory animals) is outweighed by the ‘benefit’ (the potential value of the research conducted for the improvement of human health and safety). However, while the benefits of animal research are difficult to establish or guarantee prospectively, the ethical cost in terms of animal welfare can usually be predicted, to some extent, based on previous experience from similar studies. In particular, the welfare effects of genetically modifying mice to present a phenotype of progressively debilitating disease can be estimated from the phenotypic description of these animals. The implementation of refinement (15) measures in animal experiments is intended to minimise animal distress, and hence, potentially to help tilt the cost–benefit balance to a more favourable appraisal of such experiments (16). In studies on rodent models of neurodegenerative diseases, the establishment of humane endpoints is one of the main refinement measures to reduce disease-related suffering and distress (8, 17, 18).