Kallmann Syndrome and Hypogonadotropic Hypogonadism
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Foreword

One of the major clinical advances in neuroendocrinology over the past decade has been the increasing understanding of the processes of regulation of gonadotropin-releasing hormone and its dysfunction in a clinical setting. As new regulatory peptides have been identified, the underlying causes of central hypogonadism have multiplied and the area has become increasingly complex. The reversibility of even genetically determined hypogonadotropic hypogonadism has become more firmly established, and once again clinical studies, of what used to be called 'sports of nature', have greatly expanded our understanding of basic physiological pathways. This is now an excellent point at which to take stock of the most recent progress, to put it into some form of structure, and to aid scientists and clinicians in getting to grips with this mass of new knowledge in planning future research and in treating our patients. Richard Quinton has put together a stellar group of experts in this area, and has provided a comprehensive overview of this burgeoning field. This is an excellent starting point for those caring for patients with delayed puberty, hypogonadotropic hypogonadism and other forms of central reproductive disorder, and I hope will stimulate others to work in this area.

Ashley B. Grossman, London
Preface

When I joined the research team of my friend and mentor Dr (now Professor) Pierre Bouloux back in the early 1990s, a number of things seemed evident to myself and many other investigators at the time [1]. Analysis of the relatively small number of published idiopathic hypogonadotropic hypogonadism (IHH) kindreds had long defined three mendelian modes of inheritance, X-linked recessive, autosomal dominant and autosomal recessive, so it seemed reasonable to infer the existence of at least three genes. However, nobody anticipated that the number would ever run into double figures. GNRHI was the original candidate gene for normosmic IHH, but no mutations were found in the small (by present day standards) number of patient DNAs expensively and laboriously sequenced. GNRHR did not seem to be a promising candidate, due to the near-universal responsiveness of IHH patients to exogenous GnRH pulses. KAL1, the very first IHH-related gene had just been discovered, and so it seemed that a predominantly X-linked mode of disease inheritance and/or the occurrence of de novo KAL1 germline mutations constituted a possible explanation for the observed male preponderance of cases (which, in fact, remains unexplained to this day).

The extracranial origin of GnRH neurons in the olfactory placode and their migration into the forebrain along fibres of the olfactory and (in mammals) the accessory olfactory nerves had also just been discovered. Moreover, a striking migration defect was observed in a single Xpter-deleted fetus from an X-linked Kallmann syndrome (KS) kindred. This elegant model of arrested GnRH neuron migration was assumed to underpin all forms of KS and, possibly, also of normosmic IHH (where perhaps migration arrest occurred through a mechanism independent of olfactory fibre misguidance). One consequence of universalising this model was to draw a clear line of separation between syndromic IHH and the 'functional' forms of gonadotropin deficiency that occur in relation to simple pubertal delay (like IHH, far more common in males), weight loss and stress (typically observed as hypotalamic amenorrhoea in women) and during episodes of acute illness or chronic disease. Unlike these time-limited perturbations of the GnRH pulse generator, syndromic IHH was considered to be a lifelong irreversible condition. Another was to see IHH as being entirely distinct from the primary pituitary gonadotropin deficiency observed in some syndromic forms of combined pituitary hormone deficiency.
Thinking back over these ideas and concepts, the cautionary lyrics of a famous Blues artist come to mind: ‘It ain't necessarily so...’

In many of their research grant applications, researchers in the field of IHH, including KS – its anosmic form, will have referred to how the study of this rare disease model has the potential to illuminate the processes behind normal human embryonic development and postnatal pubertal maturation. For all the truth in this statement, I suspect that many of us would admit to our primary drive being fascination with the manifestations and biological basis of IHH itself. Nevertheless, as evidenced by the following chapters from a remarkable group of contributors across the globe, it is now increasingly clear that each of the different genetic mechanisms by which IHH is caused represents a small but defined point of vulnerability to human reproductive success.

What are the evolutionary pressures that have maintained these heterozygous IHH-predisposing alleles circulating among present day human populations, such that full-blown IHH can occur in those individuals whose inherited burden of genetic defects is sufficient to critically impair neuroendocrine control of reproduction? In mammals, the capacity to grow and reproduce is intimately linked to the nutritional status. It is thus tempting to speculate that ancestral exposure to periods of sickness or famine, when it would have been counterproductive to invest scarce energy resources into reproduction and ensuing childcare, has left an imprint on our genetic lineage – of which cases of IHH may represent a tangible echo.

Finally, on behalf of myself and other investigators, I would like to offer my thanks and appreciation to those IHH patients who have allowed us into their families, as it were, to undertake detailed phenotyping and genetic analysis. Many of these individuals have experienced challenging physical and emotional lives before coming under the care of an informed and sympathetic physician or establishing contact with a patient support group. Their stories, questions and concerns can be found at www.kallmanns.org, so I will leave the final say to Neil Smith, one of its founder members:

‘My own experience of having KS and from talking to others with KS and IHH is that there is a real advantage to knowing the genetic cause behind the condition. There is an almost cathartic experience in being able to pin-point the cause of one’s condition, rather than the more common patient experience of being told ‘it just happens’. While participation in genetic studies may have no impact on current treatment, I always encourage fellow patients to take part in the hope that they can find a reason for their own condition and possibly help future generations of patients. In the not too distant future, we look forward to being able to get a rapid read-out from our DNA samples on an ‘IHH/Kallmann gene chip’.

Richard Quinton, Newcastle-upon-Tyne

Reference