Happy 20th anniversary MEN1: from positional cloning to gene function restoration

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Introduction

With this special anniversary issue on Multiple Endocrine Neoplasia Type 1 (MEN1), we celebrate not only history in the making, but also the triumph of scientific curiosity of numerous researchers and physicians around the world. This is particularly poignant these days, as we see isolationism growing stronger: the discovery and exploration of ‘Wermer syndrome’ (the original name for MEN1) reminds us once more that the spirit of ingenuity thrives most when set free without borders, neither philosophical nor physical.

We feel privileged to guest edit this special anniversary issue. The review articles cover the broad range of MEN1 syndrome and focus on the clinical (Manoharan et al. 2017, Marini et al. 2017, Sadowski et al. 2017, van Leeuwaarde et al. 2017), translational (Agarwal 2017, Alrezk et al. 2017) and basic scientific (Dreijerink et al. 2017, Feng et al. 2017, Mohr & Pellegata 2017) aspects; therefore, they provide a comprehensive update on MEN1. We are delighted that several of the scientists that pioneered MEN1 research provided their expertise to this special issue.

The history of ‘Wermer syndrome’

The initial foundation that eventually set the stage for the positional cloning of the MEN1 gene took place 63 years ago, in 1954, when the autosomal dominant inherited co-occurrence of parathyroid hyperplasia, pancreatic islet cell tumors and anterior pituitary adenoma was first proposed by the Austrian-born Paul Wermer (Wermer 1954). During that time, Wermer worked as a physician in the Department of Medicine, Columbia University, Presbyterian Hospital in New York, USA. The triad of parathyroid neoplasias, pancreatic neoplasias and pituitary adenoma (the ‘three P’s’ that every medical student learns), was reported even earlier. Harvey Cushing reported the first case with this classic MEN1 triad in 1927 (Cushing & Davidoff 1927) and Laurentius Underdahl published a case series in 1953 (Underdal 1953).

Thus, in the beginning, there was the physician’s meticulous work recognizing the prototypical abnormalities, and putting those pieces of the puzzle together. However, detailed knowledge and characterization of MEN1 was only brought about through the interactions of physicians, scientists and physician-scientists in national and international collaborative initiatives that continue to this day. Their work helped us to understand that MEN1 comprises a variety of endocrine as well as non-endocrine manifestations (i.e., adrenocortical neoplasm, thymic and bronchial neuroendocrine neoplasms, breast and soft tissue tumors) beyond the parathyroid adenoma, gastrinoma and prolactinoma described originally, and also to understand the genetic, epigenetic and post-translational mechanisms behind this disorder.

20th anniversary of the MEN1 gene cloning

Researchers around the globe successfully linked the MEN1 trait to an unknown causative gene at chromosome sub-band 11q13 by the late 1990s (Larsson et al. 1988, Bale et al. 1989) and collaborative efforts allowed the region of interest to be further narrowed down...
(Byström et al. 1990, Janson et al. 1991, Courseaux et al. 1996). The investigations supported the biallelic inactivation of the MEN1 tumor suppressor gene following the Knudson two-hit hypothesis (Bale et al. 1991, Ebrahimi & Sawicki 1997) (Fig. 1).

Finally, in 1997, two research groups, the NIH group and the European MEN1 Consortium, identified the MEN1 gene by positional cloning (Chandrasekharappa et al. 1997, Lemmens et al. 1997). We are delighted that one of the co-authors of this original publication Sunita Agarwal, then a postdoctoral fellow at the NIDDK, NIH, has graced us with an insightful and comprehensive overview on the genetic aspects of MEN1 and how these influence the clinical management of patients with MEN1 (Fig. 2) (Agarwal 2017).

Myles Brown and coworkers advance from the MEN1 gene to its protein product MENIN (Dreijerink et al. 2017). The authors review exciting recent knowledge on the functional properties of MENIN that ‘links gene-specific transcription factors to chromatin modification in a cell-specific context’. They further explore the emerging opportunities for ‘gene function restoration’ and potential therapeutic intervention of MEN1 (Dreijerink et al. 2017). Xianxin Hua and coworkers further unravel the complex interaction of MENIN with several signaling pathways (Feng et al. 2017). They provide a comprehensive update on the biochemical role and the underlying mechanism of ‘how menin controls various biological processes in neuroendocrine organ homeostasis’.

Established models are essential to elucidate MENIN mechanisms and function. Myles Brown and coworkers discuss the current cellular models available and the lack of established model systems based on human cells (Dreijerink et al. 2017). This aspect is further highlighted by an outstanding review provided by Hermine Mohr and Natalia Pellegata. These authors bring us up-to-date on the available animal models for MEN1 research and provide us with their vision for future developments (Mohr & Pellegata 2017).

The management of patients with MEN1 has changed dramatically over the last two decades. We are able to control gastric acid hypersecretion due to Zollinger–Ellison Syndrome (ZES) as one of the main causes of mortality. Today, patients are more likely to die of local or metastatic progression of neuroendocrine neoplasms. This has a tremendous impact on diagnostic as well as surveillance. Gerlof Valk and coworkers give us the physicians’ perspective and take us on a tour of how the management of MEN1-related symptoms has changed over time (van Leeuwaarde et al. 2017).

As was true over 60 years ago, comprehensive understanding of the presentation of inherited tumor traits is one of the corner stones of treating this disease. While the development of highly effective treatment modalities has allowed us to increase the life expectancy
of patients with MEN1, several reviews in this series highlight the importance of genetic counseling (Agarwal 2017, Marini et al. 2017, van Leeuwaarde et al. 2017).

In a previous article, Valk and coworkers showed that today, the correct diagnosis of MEN1 frequently remains substantially delayed. The authors point out that the ‘median lag time’ for diagnosis in family members is 3.5 years and that over 30% of non-index patients already suffer hyperparathyroidism (HPT) or duodeno-pancreatic neuroendocrine neoplasms (NEN) at the time of diagnosis (van Leeuwaarde et al. 2016). Furthermore, Valk and coworkers discuss in this same review the management of patients with clinical features similar to those observed in MEN1 patients, but for which mutation analysis has failed to detect MEN1 gene mutations.

In the same vein, Constantine Stratakis and coworkers further elucidate the importance of this ‘other’ MEN1 syndrome. In their review, the authors outline the genetics, clinical manifestations and management of patients with the closely related MEN4 syndrome, caused by germline mutations in the gene (CDKN1B) coding for p27 that result in the development of parathyroid and pituitary adenomas (Alrezk et al. 2017).

While the development of hormone assays which began in the late 1960s allowed us to better identify patients affected by MEN1-related tumors, modern imaging helps us to visualize even hormone-inactive tumors at much earlier stages. The review on therapeutic approaches and management of MEN1 by Detlef Bartsch and coworkers highlight the changes that have taken

Figure 2
Group photo of the MEN1 gene team outside NIH building 49 where the team met for weekly group meetings. The gene team included (in the front row, from left to right) S Agarwal (NIDDK), Z Zhuang (NCI), S Chandrasekharappa (NHGRI), S Olufemi (NHGRI), S Guru (NHGRI); (in the second row, from left to right) M Kester (NIDDK), M Boguski (NCBI/NLM), Y Kim (NIDDK), S Marx (NIDDK), J Crabtree (NHGRI); (in the third row, from left to right) M Emmert-Buck (NCI), L Debelenko (NCI), J Weisemann (NCBI/NLM), P Manickam (NHGRI); (in the back row, from left to right) A Spiegel (NIDDK), J Lubensky (NCI), C Heppner (NIDDK), L Burns (NIDDK), F Collins (NHGRI). Not shown are L Liotta (NCI), Y Wang and B Roe (University of Oklahoma), and Q Dong (NIDDK, later at University of Sydney, Australia). The image was kindly provided by S Agarwal from ‘The NIH Record’ Newsletter May 20, 1997. Vol. XLIX, No. 10.
place in diagnosis, and in particular, imaging of MEN1-associated tumors (Manoharan et al. 2017). The authors discuss the modalities and timing for MEN1 surveillance and highlight the development and importance of novel imaging techniques. Furthermore, since small non-functioning NEN have become the most common pancreatic NEN (PNEN), the authors address the question of how to deal with small pancreatic neoplasms.

The concept of active surveillance is discussed not only by Bartsch and coworkers but also by other reviews in this series (Marini et al. 2017, Sadowski et al. 2017, van Leeuwaarde et al. 2017). A large international collaborative initiative has very recently shown that non-functioning PNEN below 2 cm in size harbor a low oncologic property. During the study period, active surveillance of patients with these tumors increased from 36% (1997–2007) to 64% (2007–2013). Importantly, only 36% of patients under surveillance required surgery during follow-up (Triponez et al. 2017).

MEN1 management has shifted to patient-centered, individualized treatment and the follow-up management is becoming more and more important. Treatment options are carefully compared for risk and benefit, and tailored to patient needs by an interdisciplinary tumor board together with the patient in a ‘shared decision-making’ process, as van Leeuwaarde and coworkers state in their review. This concept is further expanded upon by Maria Luisa Brandi and coworkers, who provide us with an outstanding review of the evolution of clinical practice guidelines over time that sets the stage for discussions of how quality of life is affected in MEN1 patients. This review outlines how the individualization and personalization of treatment options, especially surgical intervention, affects quality of life (Marini et al. 2017).

Frédéric Triponez and coworkers focus on surgical management of patients with MEN1. In particular, they highlight the important management of neuroendocrine tumors (pancreatic, thymic and bronchial) and of aggressive/metastatic disease (Sadowski et al. 2017). The most frequent endocrinopathy in MEN1 is HPT that occurs in over 80% of patients. Brandi and coworkers discuss the management of these patients and how these treatment algorithms have changed over time (Marini et al. 2017). For pituitary adenoma, which occurs in 10% of patients with MEN1, there are insufficient data at this point to propose a surgical management that differs from that of sporadic pituitary tumors. Similarly, the surgical treatment of other MEN1-associated tumors broadly follow the treatment modalities for their sporadic counterpart.

Multiple endocrine neoplasia type 1, aka Wermer syndrome, remains a fascinating tumor syndrome. For the clinician, rapid recognition and diagnosis, quality of life, active surveillance and improvements in genetic counseling are emerging as critical aspects of care. Our diagnostic and therapeutic modalities will further be refined to reduce risk and maximize benefit. As we start to understand the functional properties of MENIN, new aspects of its functions and implications in disease are emerging that require further elucidation. Finally, these findings will eventually be translated to further inform clinical management algorithms and provide us with new therapeutic or even better, preventative, options.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this editorial.

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