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REVIEW ARTICLE

Living with Legacy: Outcomes and Future Implications for Offspring of Patients with MEN1

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Abstract

Background. Multiple endocrine neoplasia type 1 (MEN1) is a hereditary condition with an autosomal dominant inheritance, with a predisposition to both endocrine and non-endocrine tumours. MEN1-related tumours can appear as early as the age of five, with disease penetrance increasing with age. Offspring of a MEN1 parent shows a 50% probability of inheriting the MEN1-related gene mutation. A MEN1 diagnosis in a parent can lead to significant anxiety for both the diagnosed parent and their undiagnosed at-risk children. There is limited consensus specific for managing offspring of individuals diagnosed with MEN1.

Objectives. This review aims to evaluate the existing literature on the outcomes of MEN1 syndrome in the offspring of affected patients, to identify gaps in current protocols and to suggest possible improvements.

Methodology. A literature review was conducted to examine the outcomes and characteristics of the offspring of individuals diagnosed with MEN1.

Results. Predictive testing and screening for organ involvement in MEN1 aid early diagnosis and timely interventions. DNA testing is recommended for children within the first decade of life, and screening for organ involvement should ideally begin at age 5 years for all MEN1 mutation carriers. Manifestations of MEN1 in younger children are different from those of affected adults.

Conclusions. Standardised, internationally-accepted guidelines that provide specific recommendations for screening, diagnosis and treatment of offspring of adults diagnosed with MEN1 is a timely need. Furthermore, the absence of national and international data pooling across regions remains a serious limitation, impeding the ability to draw conclusions from larger, more representative patient populations.

Key words: MEN1, endocrine tumours, at-risk offspring, inheritance, genetic screening

INTRODUCTION

Multiple endocrine neoplasia type 1 (MEN1) is a rare autosomal dominant hereditary tumour syndrome resulting from inactivating mutations in the tumour suppressor gene MEN1, and is distinguished by a predisposition to various endocrine and non-endocrine tumours.[1] The condition typically consists of hyperplasia and/or tumours originating from the parathyroid, duodeno-pancreatic and/or anterior pituitary glands, which are seen in 90%, 30–70%, and 30–40% of individuals, respectively, by the age of 40, but also includes other manifestations such as collagenomas and lipomas.[2,3] MEN1-associated neoplasms have been identified as early as at the first five years of life. However, most diagnoses occurred after age 10, with disease penetrance increasing with advancing age.[2] Despite advances in the diagnosis and management of MEN1-associated tumours, individuals with this disease still exhibit a reduced life expectancy relative to the general population, with a mean age of mortality ranging from 55 to 60 years.[4,5]

Screening for MEN1 presents with unique challenges, since the combination of affected glands can vary among members of the same family, and there is little genotype-phenotype correlation.[1] The precise age-related penetrance, which

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refers to the proportion of carriers of the gene mutation who have shown symptoms or signs of the disease by a certain age, is still to be determined.[6] Moreover, a delayed diagnosis of MEN1 has been linked to increased morbidity, mostly associated with metastatic neuroendocrine tumours (NETs), as there is a median lag time of 3.5 years between the diagnosis of MEN1 in the index case and the genetic testing of family members for the condition.[7,8] In 50–70% of patients with MEN1, mortality is attributable to the disease itself.[9,10] Clinical practice guidelines for managing MEN1 were recently published in 2025 with modifications to the previous guidelines published in 2012.[3,11]

Why is it important to study the offspring of patients with MEN1 syndrome?

Psychological and social impact of early diagnosis of MEN1 in children

The diagnosis of MEN1 in a parent can significantly influence family dynamics. The parent already diagnosed with MEN1 as well as the yet-undiagnosed children may both suffer significant anxiety and concern regarding developing health risks associated with potential MEN1 in the offspring.[12,13] The chronic nature of the disorder, the need for long-term regular screening until a tumour(s) is detected, ongoing treatment for the diagnosed tumour (s), and the constant monitoring for risk of recurrence of a treated tumour(s) can significantly impact the quality of life for patients and their families. The presence of MEN1 in an individual or a family is a lifelong condition that a diagnosed individual and their family must live with. In addition to the psychological stress and anxiety associated with the disease, it also poses a significant financial burden associated with lifelong screening and monitoring, especially in resource poor settings. Early diagnosis of MEN1 in children can cause significant psychological and social impact on the child. The recommendation is to start screening children of affected parents at the age of 5, which is an age where they are unlikely to have an understanding of the disease condition and the need for frequent screening.[3] Frequent hospital visits, testing and treatment can lead to missed school days and childhood events with friends, leading to disappointment, which the child may find difficulty to understand. Affected children can experience anxiety from peer rejection and have difficulties fitting in.

Early screening strategies and psychological and social support for children and families with MEN1

Transparent discourse on illness and its ramifications is essential for the emotional welfare of such children and young adults. Providing education on MEN1, along with early screening and implementing a comprehensive follow-up plan, helps to alleviate anxiety in both parents and children of families affected with MEN1.[13] While coping mechanisms to unexpected new diagnosis and the effect of the disease on the children may differ in each family, there are patient groups or counselling services that offer a venue for exchanging experiences, sharing information regarding

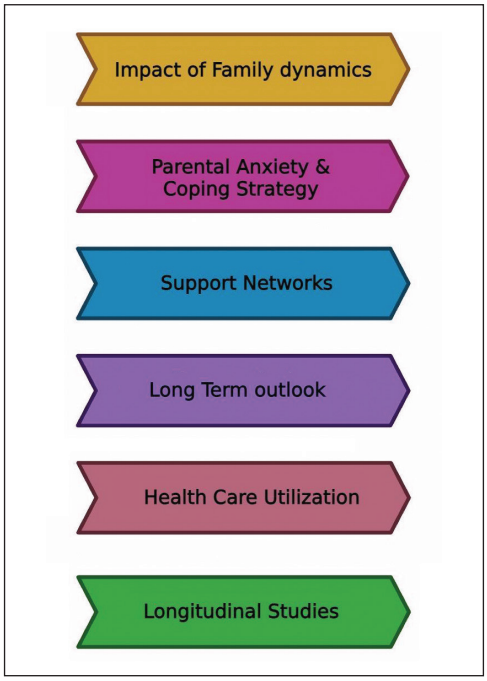

Figure 1. Key considerations in researching offspring of MEN1 patients.

MEN1 and providing some support to affected families.[13] Establishing a supportive environment in which children feel at ease expressing their fears and concerns is essential. These networks may encompass healthcare practitioners, counsellors and peer support groups, that can offer essential information and emotional assistance.[12] AMEND (*Association for Multiple Endocrine Neoplasia Disorders*) is a support group in the United Kingdom focused on individuals with MEN syndromes. They offer child-friendly guides and pamphlets, often in a cartoon or graphic form, aimed to explain and reassure.[14] The quality of life of the children of individuals with MEN1 may be influenced by the apprehension of developing the disorder, or the actual experience of living with a genetic illness. Longitudinal studies are essential for comprehending the impact of these factors on overall well-being.[15] This review aims to evaluate existing literature on the outcomes of MEN1 syndrome in the offspring, to identify gaps in current protocols, and to suggest possible improvements. (Figure 1)

METHODOLOGY

This narrative review on the offspring of individuals with Multiple Endocrine Neoplasia Type 1 (MEN1) entailed a systematic literature search across multiple databases, including PubMed, Embase, Scopus, and Google Scholar, employing keywords such as "MEN1 syndrome," "offspring" and "outcome." The inclusion criteria targeted studies on the progeny of MEN1 patients, including clinical studies, observational studies and case reports published in peer-reviewed publications over the past three decades. The exclusion criteria were papers that were not immediately pertinent to MEN1 or its implications for progeny, along with non-English literature lacking accessible abstracts.

Data extraction was done with a standardised form to collect essential information, including study design, demographics, clinical findings, screening processes and outcome.

Genetics and inheritance of MEN1

MEN1 syndrome is inherited in an autosomal dominant manner, and each offspring of an affected parent has a 50% chance of inheriting the mutation. The MEN1 gene is located on chromosome 11q13, and the related tumorigenesis is according to Knudson's 'two hit' hypothesis, indicating a gene inactivation. More than 1000 germline MEN1 mutations have been identified, of which 1% to 3% are large deletions. These mutations predict absent or truncated menin. Around 90% of individuals diagnosed with MEN1 have an affected parent, indicating a familial form of MEN1, defined as having at least one first-degree relative having one or more main endocrine tumours, or involvement if only one endocrine organ along with a MEN1-causing germline mutation. There are instances where a family history in familial MEN1 may not be identified because of either failure to recognise the disorder in an affected family member, early death of a parent before the onset of symptoms, or late onset of the disease in the affected parent. If the disease-causing MEN1 germline mutation identified in the proband is not identified in either parent, the possibilities are a germline mosaicism in a parent, or a *de novo* mutation in the proband. Simplex MEN1 due to *de novo* mutations, rather than familial MEN1, is seen in 10% of MEN1 cases. DNA testing detects MEN1 mutations in 80 to 90% probands with familial MEN1, and in 65% probands with simplex MEN1. When a known MEN1-causing mutation is not identified in an individual in a family with more than one affected family member in two generations, the next possible test would be linkage or haplotype analysis. Simplex MEN1 cases are less likely to be positive for a mutation than in familial cases, because some simplex cases are caused by somatic mosaicism.[16] One should also be aware of 'phenocopies' of MEN1 when there are incidentally two endocrine tumours identified in an individual who is clearly MEN1-mutation negative.

Genetic anticipation in successive generations

MEN1 mutations have a high penetrance of more than 95% including age-related penetrance. Genetic anticipation in MEN1 has been identified in some cases, but its mechanisms have not been fully explored and described. Genetic anticipation refers to the phenomenon of decreased age of disease onset or an increased severity in successive generations, indicating a higher mortality and morbidity from MEN1 in offspring and successive generations. Genetic anticipation has been well-described in heritable cancer syndromes such as dyskeratosis congenita, Lynch syndrome, Li-Fraumeni syndrome, Von Hippel-Lindau syndrome and hereditary breast and ovarian cancer syndrome. Three potential hypothesised mechanisms have been described in the literature for genetic anticipation in MEN1. The first speculated mechanism is progressive telomere shortening in successive generations, possibly owing to haploinsufficiency of the affected gene. The second hypothetical mechanism is the progressive accumulation of germline mutations prior to the loss of heterozygosity, due to microsatellite instability in germ cells passing on mutant alleles to offspring. The third possible mechanism is accumulation of DNA copy number variations in the context of haploinsufficiency.[17]

When is the best time to test offspring?

Predictive testing and screening for organ involvement helps with early diagnosis and facilitates interventions that reduce morbidity and mortality associated with MEN1. A DNA test identifying an individual as a MEN1 mutant gene carrier does not usually lead to immediate medical or surgical treatment, but it suggests the need for regular and frequent clinical screening. Identifying carriers also allows reproductive planning choices. However, predictive testing can have psychological ramifications, especially in asymptomatic individuals. Therefore, genetic counselling and patient education should precede carrier testing. Parents with MEN1 should have an initial consultation with a pediatric endocrinologist with or without the child, when the child is 5 years of age to discuss shared decision-making regarding screening and surveillance plans.[11] A DNA test for genetic testing of offspring in MEN1 is recommended to be offered to children within the first decade of life, as some tumours such as insulinomas and pituitary tumours are known to develop in children as early as at 5 years of age.[16] However, one always needs to bear in mind parental concerns regarding the impact of testing on the child, and possible implications regarding life insurance and mortgage applications in adulthood.

The current clinical practice guidelines recommend to start clinical screening for organ involvement manifestations from the age of 5 years in all MEN1 mutation carriers, and to further expand the screening with advancing age, with biochemical screening of asymptomatic children from 10 years.[3,11] In instances where molecular genetic testing is not possible or not informative, individuals at 50% risk of a MEN1 mutation, indicated by having first-degree relatives with MEN1 syndrome, should undergo routine biochemical and clinical evaluation.[16] The current MEN1 clinical practice guidelines recommend initiating clinical screening for pituitary tumours and insulinoma from 5 years of age, and regular biochemical assessments 10 years of age, with assessment for bronchial and thymic carcinoids at 15 years of age and gastrinomas at 20 years of age. Clinical, biochemical and imaging screening for MEN1-associated NETs is performed at regular intervals, generally annually. The frequency of screening investigations depends on the NET risk of occurrence and aggressiveness, with screening frequency increasing with advancing age.[3,11] Serum calcium levels should be tested every 1 to 3 years from the age of 10 years onwards to screen for primary hyperparathyroidism in children and adolescents (<19 years), and is increased

to annually in adults.[11] While physical examination for growth and pubertal development should be done in children with MEN1, asymptomatic children with normal growth and development should undergo biochemical screening for pituitary NETs with serum prolactin and insulin like growth factor -1 (IGF-1) from the age of 10 years, repeated every 1 to 3 years, compared to the previous recommendation of 5 years of age.[3,11] There is no consensus regarding testing gastrin level in children until they reach 18 years of age. Insulin level testing in children is done only if they develop symptomatic hypoglycaemia.[11] Although there is no consensus on the benefit of pituitary MRI screening in asymptomatic children with normal growth and development, if a decision for MRI pituitary is made by shared decision making, the age for first MRI pituitary is considered at 15 years, repeated every 3 to 5 years if negative.[11] The first MRI to screen for duodeno-pancreatic neuroendocrine tumours (DP-NETs) in asymptomatic children is recommended at 10 to 15 years of age, followed by repeat scans every 2 to 3 years if negative.[11] The 2012 guidelines recommended commencing thoracic imaging for thoracic NETs in asymptomatic individuals with MEN1 at age 15 years, but the recent 2025 guidelines have delayed this age to 20 to 25 years preferably with computed tomography (CT).[3,11]

Management of pre-symptomatic neuroendocrine tumours detected on screening

Asymptomatic children and adolescent or young adults (AYA) diagnosed with primary hyperparathyroidism without evidence of target organ involvement can undergo active surveillance. However, if they become symptomatic, develop end-organ involvement or have a total serum calcium level >1 mg/dL (>0.25 mmol/L) consistently above the upper limit of the normal range, subtotal (3 to 3.5 glands) parathyroidectomy with transcervical thymectomy is recommended. Early parathyroidectomy for primary hyperparathyroidism can be considered in the presence of concomitant symptomatic gastrinoma, as this would help with reducing gastrin hypersecretion and gastrinoma tumour growth.[11]

The treatment of clinically functional and symptomatic MEN1-associated NETs is surgical resection and additional medical management as needed. However, the optimal treatment strategy remains controversial for non-functional NETs or earlier detected NETs in their pre-symptomatic stage during screening. Upon detection of a non-functional NET in their pre-symptomatic stage, the decision regarding early intervention or active surveillance depends on the aggressiveness of the tumour, as indicated by its size and rate of growth. The risk of metastasis of NETs increases substantially when the tumour size exceeds 2 cm, with most smaller tumours running an indolent course. In MEN1 patients with stable non-functional pancreatic NETs ≤2 cm in size with growth rates <1 mm/year (for >1 year), active surveillance with serial imaging every 1 to 2 years is recommended.[11] Consideration of surgery is recommended for NETs larger than 1 cm.[3] However, this size criterion in decision-making cannot be applied to all NETS, especially in the absence of specific tumour biomarkers for aggressiveness. Bronchopulmonary NETs generally have a low growth rate and excellent overall survival compared to other MEN1-associated NETs. Serial imaging, preferably with non-contrast magnetic resonance imaging (MRI), given its low radiation exposure, is recommended to ascertain the rate of tumour growth. Given that occasionally small non-functional NETs <1 cm in size can also develop metastasis, ^{68}Gallium DOTATATE PET/CT may be of value in detecting occult metastatic disease. However, it has limited utility as a serial surveillance investigation due to its high ionising radiation exposure and expense. The risk of ionising radiation exposure with any of the aforementioned imaging modalities, when performed in regular intervals, is specifically harmful for growing children. Therefore, it is crucial to have specific strategies for children in surveillance of small, non-functional NETs.[18]

Differences in MEN1 manifestation in children with MEN1 compared to adults with MEN1

The frequency of MEN1-related tumours in children is different to that of adults. Primary hyperparathyroidism was the most common clinical manifestation of MEN1 in both children and adults; however the second most frequent manifestation in children is a pituitary tumour, followed by a gastro-entero-pancreatic neuroendocrine tumour. MEN1-related pituitary tumours are more frequent in adult females. There is a higher penetrance of non-functioning pituitary tumours (42%) than insulinomas (11%) in MEN1 patients aged 12 to 20 years. Cushing's disease is more common than adrenal Cushing's in childhood MEN1.[15]

Clinical studies conducted on the children of patients with MEN1

A study conducted in Japan discovered three asymptomatic mutant gene carriers (children of cases 1-3) and 12 non-carriers among first-degree relatives of sporadic patients with the MEN1 mutation. No non-carriers exhibited MEN1-related lesions.[19] Another case study in this research indicated that the parents did not possess the same mutation, implying a *de novo* mutation in the offspring. One of the proband's daughters was identified as an asymptomatic carrier of the mutation, and the patient's genotype aligned with the biological parentage of her mother and father. Haplotype analysis surrounding the MEN1 region indicated that the patient's mutant allele originated from her father, verifying that the detected mutation 893+1G-A was not *de novo*[19] (Table 1).

An Indian case study revealed that the proband's elder brother died due to a pituitary tumour, while his sister had nephrolithiasis associated with hyperparathyroidism, causing hypercalcaemia,which was treated with excision of a parathyroid adenoma.[20] His parents and his three children, the eldest being 13 years old, and his sister's two

Table 1. Global clinical studies on offspring of MEN1 patients: A comparative analysis

Country, Year Of Publication	Methodology	Results	Conclusion/Recommendation	Reference
Japan, 1999	10 cases of diagnosed Japanese MENl were included.	Identified 3 asymptomatic mutant gene carriers (children of cases 1-3) and 12 noncarriers among first-degree relatives of the sporadic patients with MENl	A patient who has been considered sporadic will become a proband of familial MEN1. If no offspring have inherited the mutant allele, or while offspring inheriting the mutant allele are too young to manifest symptoms, or if a family study is insufficient, the diagnosis will remain as sporadic MEN1.	18
India, 2008	A case study of an Indian family with MEN1 syndrome	The DNA sequencing of exon 4 of the patient's family members showed the presence of the same mutation in 7 of 8 cases examined. The father did not carry the mutation; the mother was the carrier. Apart from the proband, the daughter and 5 of 6 grandchildren were affected.	The genetic testing is shown to improve the quality of diagnosis and treatment in the proband and family members.	19
United Kingdom, 1996	Age related penetrance was Investigated. 709 people from 62 MEN1 families, and 36 non- familial MEN1 patients	Among 288 offspring of 101 affected parents, 129 were affected. The ages of conversion from an unaffected to affected phenotype were found in two individuals to be 20 and 21 years respectively, 2/162 carriers remain unaffected, thereby indicating a 98.8% penetrance of the MEN1 gene by the age of 53 years.	Screening should be initiated before 8 years of age.	6
Netherlands, 2020	Mutation Positive MEN1 families. A total of 10 families was included	The number of affected family members ranged from 11 to 29 per family. A total of 137 affected members (90.1%) showed 1 or more MEN1-related manifestations during follow-up. The median age at detection of the first encountered manifestation was 46 in the first generation, compared with 14 (range: 11–17 years) in the youngest generation. Furthermore, patients from younger generations encountered their first MEN1-related tumor significantly earlier in life.	Manifestations occurred significantly earlier in the lives of patients from successive generations. Even with the adjustments for the beneficial effect of surveillance programs, our results suggested the presence of genetic anticipation in MEN1.	16
France, 1997	Two branches of a MEN1 family were studied.	Clinically, generations IV and V were severely affected with the disease. In generation IV of the first branch, 5 siblings out of 7 were affected.	By comparing the age of presentation and the severity of the disease through each generation, there is evidence of anticipation phenomenon.	20
Tasmania, 2019	Retrospective cohort analysis of 341 children with a MEN1 positive (MEN1+) parent and n = 314 children with MEN1 negative (MEN1–) parents. The contemporary cohort included neonates (n = 52) of MEN1+ women (n = 21)	Historical cohort: compared with MEN1– parents, children of MEN1+ parents were more likely to die postpartum at 6 months of age). Excess mortality at 15 years of age was observed for children of MEN1+ mothers and fathers. Contemporary cohort: neonates of MEN1+ mothers were more likely to have low birth weight)	Children with a MEN1+ parent are disproportionately vulnerable postpartum. Neonates of MEN1+ mothers remain vulnerable despite contemporary care. The excess risk was not fully explained by maternal MEN1 or antenatal hypercalcemia.	21

children, remained asymptomatic. DNA sequencing of exon 4 in the patient's relatives revealed the identical mutation in 7 out of 8 tested cases. The mother was the carrier, while the father did not possess the mutation. In addition to the proband, the daughter and 5 of the 6 grandchildren were mutation-positive. The proband's eldest child was found to have elevated serum calcium and an insulinoma[20] (Table 1).

The implementation of standardised surveillance methods and clear criteria for MEN1 symptoms has improved follow-up for subsequent generations. However, older generations have benefited less from these techniques, leading to potential delays in diagnosis compared to more recent generations. In the family studied, the second and third generations showed no clinical signs of MEN1, while the fourth generation had eight affected individuals. The fifth generation had all 5 patients show at least one MEN1-related symptom before the age of 22[20] (Table 1).

Transition of care of adolescents and young adults with MEN1

MEN1 is a chronic disorder which requires lifelong surveillance and ongoing treatment. This requires a thorough understanding of the disease condition and is a major responsibility for the patient. Children with MEN1 are managed by a paediatric endocrinologist, and they are primarily cared for by their parents, who assume the principal responsibility for their follow-up care and decision-making. When transitioning an AYA with MEN1 to adult care, they need to gradually be helped to take responsibility for their care and decision-making. Unfortunately, individuals with rare endocrine disorders, including MEN1, have been shown to have a high drop-out rate during transition of care, leading to loss of follow-up and active surveillance. Transition of care must be done gradually over a period of time and should commence at an earlier age. This is to ensure that the AYA gets a better understanding of the disease, understands the responsibility

that comes with it, and develops confidence with self-care and independent decision-making. This transition process should include joint consultations with paediatric and adult endocrinologists, as well as the MEN1-affected child and their parents. Before the complete transition of care, the AYA's readiness for transition should be assessed. This can be done through validated checklists, such as the TRAQ (Transition Readiness Assessment Questionnaire) and TRAM (Transition Readiness and Appropriateness Measure). It is important to identify shortcomings early, so that patients have sufficient time to train all skills with any required support from the endocrinologist prior to transfer.[23] This is especially important as the AYA considers moving out of the parental home to attend college or university, when close parental supervision is no longer possible.

Pregnancy outcomes

Managing MEN1-related complications in pregnancy can be challenging. Primary hyperparathyroidism (PHPT) during pregnancy correlates with a significant risk of maternal, fetal and neonatal adverse effects, directly proportional to maternal calcium levels. This can result in intrauterine growth restriction, preterm delivery, intrauterine fetal demise, neonatal low birth weight and hypocalcaemia.[24,25]

Children with an MEN1-positive parent have historically been shown to experience an excess of mortality, with the risk most pronounced in the post-partum period.[22] In the contemporary context, offspring of MEN1-positive mothers experienced a high frequency of adverse events during the neonatal period, including low birth weight, prolonged length of hospital stay, increased admission to higher dependency nurseries and metabolic and infectious events. Antenatal hypercalcaemia alone did not significantly alter neonatal outcomes. Hypoglycaemia was highly prevalent in neonates of MEN1-positive mothers, and this may reflect an additive risk posed by increased incidence of low birth weight, preterm birth and antenatal diabetes.[22] MEN1 is associated with an increased risk of type 2 diabetes mellitus. The excess of childhood mortality in the historical cohort was not solely attributable to offspring of MEN1-positive mothers but was also apparent in offspring of MEN1-positive fathers.[22]

Key issues and debates in offspring of multiple endocrine neoplasia type 1

Inadequate protocols and guidelines

Existing Protocols and International guidelines, including the European Society of Endocrinology (ESE) guideline and the American Association of Clinical Endocrinologists (AACE) Clinical Practice Guideline relating to MEN1, have been created with an emphasis on managing adult patients diagnosed with the condition, including recommendations for the management of related tumours.[3] These guidelines advocate for the screening of pituitary tumours, parathyroid hyperplasia, and pancreatic neuroendocrine tumours at an early age, although they typically do not include explicit recommendations for the offspring of individuals affected with MEN1. This constitutes a significant limitation in guidelines, as MEN1 may manifest earlier in life, and unaddressed early symptoms in children could be more severe.

Adult MEN1 patients generally undergo screening beginning in their late teens or early twenties. However, there is no consensus on the optimal age to initiate screening for offspring, though evidence shows the benefit of initiating screening before the age of 8 years.[20] There is also no consensus on the specific treatments recommended for this population. This ambiguity arises partly from the diversity in disease manifestation and penetrance, which can significantly differ among individuals, even within the same family.[26]

Certain specialised institutions, such as neuroendocrine tumour centres (NET centres), have established different protocols for the management of MEN1 patients, potentially better suited to the unique requirements of at-risk children and adolescents.[27] These centres may do early genetic testing, increase surveillance frequency, and tailor therapies according to genetic results. Nonetheless, these procedures lack widespread adoption and standardisation, resulting in significant variations in institutional practices compared to larger international recommendations. As a result, there is a lack of a standardised method for offspring management, resulting in disparities in treatment and outcomes.

Data gaps and challenges

Owing to the lack of national or worldwide data pooling, MEN1 research remains fragmented and isolated. Researchers from various regions may face the challenges of working with limited sample sizes, which limits the generalisability and impact of their findings. Even if national data are obtained, many nations lack the legal frameworks and ethical principles required for the secure and standardised exchange of health data across borders. This limitation restricts the ability to aggregate MEN1 data internationally or regionally, which could improve research and inform clinical decision-making. The lack of longitudinal data on the emergence of MEN1 offspring impedes the establishment of effective management procedures. The majority of research concentrates on adults with established tumours, providing scant information on pre-symptomatic individuals or those diagnosed at a younger age.[3,11] Consequently, there is limited knowledge regarding the early natural history of MEN1 in infants and adolescents, as well as the potential effects of early therapies on disease progression.

Recommendations and future directions

Future guidelines for the management of offspring of individuals with MEN1 in developing countries should emphasise improving accessibility and support. Community-oriented genetic counselling should be imple-

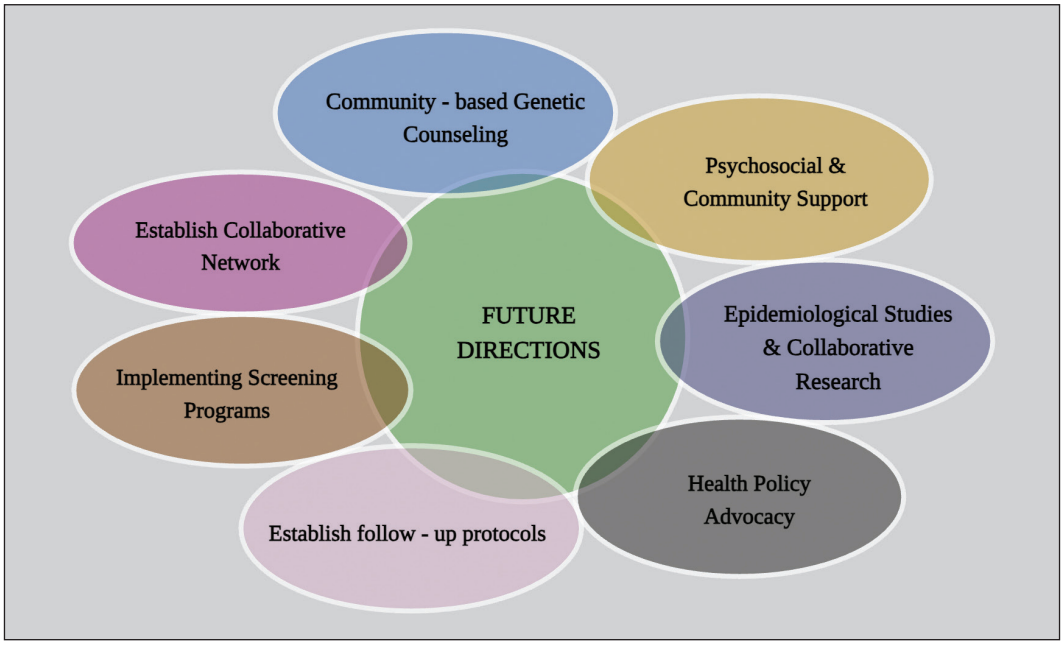

Figure 2. Key aspects for future research on offspring of MEN1 patients.

mented, with local healthcare professionals educated to deliver customised support and information. Enhancing access to affordable genetic testing is essential, possibly via subsidies and mobile health units that serve underserved regions. Comprehensive screening systems must be established, incorporating early detection techniques into current maternal and child healthcare. As psychosocial assistance is crucial, healthcare providers must undergo mental healthcare training, and local support networks should be established to promote community involvement. To enhance the management of offspring of patients with MEN1, it is imperative to establish a collaborative framework for data aggregation and the formulation of comprehensive clinical guidelines. Specialised institutions, such as Neuroendocrine Tumour (NET) Centres, play a vital role in enhancing therapeutic protocols for the management of MEN1. These centres serve as focal points for research, education, and the dissemination of best practices, ensuring that healthcare personnel possess the most updated knowledge and tools for patient management.

Moreover, the requirement for global collaboration and data exchange among academics and institutions is essential. Collaborative initiatives can enhance worldwide comprehension of MEN1, leading to improved clinical outcomes through the exchange of resources, expertise and data. Creating national databases that aggregate clinical, genetic and psychosocial data on MEN1 can increase understanding of the condition's prevalence and presentations across various groups. These databases should be structured to facilitate seamless access for healthcare professionals and researchers, thereby enhancing informed decision-making and evidence-based practice. Multiple domains necessitate further inquiry to improve our comprehension of MEN1, especially regarding its effects on offspring. Research should concentrate on the long-term health consequences for these individuals, the psychosocial impacts of residing with a hereditary illness, and the efficacy of early screening techniques. Furthermore, research on the genetic differences and environmental factors that affect MEN1 expression across diverse populations is essential. Promoting the incorporation of genetic disorders in national health strategies will guarantee the allocation of adequate resources. Management plans must be culturally relevant and tailored, taking into account the socio-economic circumstances of families. Ultimately, sustained health monitoring, possibly through telemedicine and digital platforms, can provide continuous assistance and early identification of potential MEN1-related illnesses, ensuring a holistic approach to the health and welfare of these individuals (Figure 2).

CONCLUSION

The study of the offspring of patients with MEN1 is an important area of research that has been largely under-explored, particularly in less developed nations. This review has identified major gaps in our understanding of MEN1 in children and adolescents, with a particular emphasis on the absence of comprehensive screening methods, standardised management practices and adequate psychosocial support for affected families. We emphasise the need for standardised, internationally accepted guidelines that not only address the clinical care of MEN1 in adults, but also provide clear recommendations for the screening, diagnosis and therapy of affected children. Furthermore, the lack of national and international data pooling remains a significant limitation, hindering our ability to draw conclusions from larger, more representative patient populations.

Statement of Authorship
All authors fulfilled ICMJE authorship criteria.

CRediT Author Statement

DTM: Conceptualization, Methodology, Validation, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration; **KPJ:** Conceptualization, Methodology, Validation, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Project administration; **GW:** Conceptualization, Methodology, Validation, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization; **AG:** Conceptualization, Methodology, Validation, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision.

Data Availability Statement

Datasets generated and analyzed are included in the published article.

Author Disclosure

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References

1. Chandrasekharappa SC, Guru SC, Manickam P, et al. Positional cloning of the gene for multiple endocrine neoplasia-type 1. Science. 1997;276(5311):404-7. PMID: 9103196 DOI: 10.1126/science.276.5311.404
2. Goudet P, Dalac A, Le Bras M, et al. MEN1 disease occurring before 21 years old: a 160-patient cohort study from the Groupe d'Etude des Tumeurs Endocrines. J Clin Endocrinol Metab. 2015;100(4): 1568-77. PMID: 25594862 DOI: 10.1210/jc.2014-3659
3. Thakker RV, Newey PJ, Walls GV, et al. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). J Clin Endocrinol Metab. 2012;97(9):2990-3011. PMID: 22723327 DOI: 10.1210/jc.2012-1230
4. Ito T, Igarashi H, Uehara H, Berna MJ, Jensen RT. Causes of death and prognostic factors in multiple endocrine neoplasia type 1: A prospective study: comparison of 106 MEN1/Zollinger-Ellison syndrome patients with 1613 literature MEN1 patients with or without pancreatic endocrine tumors. Medicine (Baltimore). 2013;92(3):135-81. PMID: 23645327 PMCID: PMC3727638 DOI: 10.1097/MD.0b013e3182954af1
5. Norton JA, Krampitz G, Zemek A, Longacre T, Jensen RT. Better survival but changing causes of death in patients with multiple endocrine neoplasia type 1. Ann Surg. 2015;261(6):e147-8. PMID: 26291955 DOI: 10.1097/SLA.0000000000001211
6. Trump D, Farren B, Wooding C, et al. Clinical studies of multiple endocrine neoplasia type 1 (MEN1). QJM. 1996;89(9):653-70. PMID: 8917740 DOI: 10.1093/qjmed/89.9.653
7. van Leeuwaarde RS, van Nesselrooij BPM, Hermus AR, et al. Impact of delay in diagnosis in outcomes in MEN1: Results from the Dutch MEN1 study group. J Clin Endocrinol Metab. 2016;101(3):1159-65. PMID: 26751192 DOI: 10.1210/jc.2015-3766
8. de Laat JM, van Leeuwaarde RS, Valk GD. The importance of an early and accurate MEN1 diagnosis. Front Endocrinol (Lausanne). 2018;9:533. PMID: 30254610 PMCID: PMC6141626 DOI: 10.3389/fendo.2018.00533
9. Dean PG, van Heerden JA, Farley DR, et al. Are patients with multiple endocrine neoplasia type I prone to premature death? World J Surg. 2000;24(11):1437-41. PMID: 11038219 DOI: 10.1007/s002680010237
10. Doherty GM, Olson JA, Frisella MM, Lairmore TC, Wells SA, Norton JA. Lethality of multiple endocrine neoplasia type I. World J Surg. 1998;22(6):581-7. PMID: 9597932 DOI: 10.1007/s002689900438
11. Geerdink EA, van der Luijt RB, Lips CJM. Do patients with multiple endocrine neoplasia syndrome type 1 benefit from periodical screening? Eur J Endocrinol. 2003;149(6):577-82. PMID: 14641000 DOI: 10.1530/eje.0.1490577
12. Brandi ML, Pieterman CRC, English KA, et al; Delphi Expert Panel. Multiple endocrine neoplasia type 1 (MEN1): Recommendations and guidelines for best practice. Lancet Diabetes Endocrinol. 2025; 13(8):699-721. PMID: 40523372 DOI: 10.1016/S2213-8587(25)00119-6. Erratum in Correction to Lancet Diabetes Endocrinol. 2025; 13: 699-721. Lancet Diabetes Endocrinol. 2025;13(11):e14. PMID: 40976253 DOI: 10.1016/S2213-8587(25)00293-1.
13. Baynam G, Gomez R, Jain R. Stigma associated with genetic testing for rare diseases—Causes and recommendations. Front Genet. 2024; 15:1335768. PMID: 38638122 PMCID: PMC11024281 DOI: 10.3389/fgene.2024.1335768
14. Strømsvik N, Nordin K, Berglund G, Engebretsen LF, Hansson MG, Gjengedal E. Living with multiple endocrine neoplasia type 1: Decent care–insufficient medical and genetic information, a qualitative study of MEN1 patients in a Swedish hospital. J Genet Counsel. 2007; 16(1):105-17. PMID: 17277996 DOI: 10.1007/s10897-006-9047-2
15. AMEND. AMEND: The Association for Multiple Endocrine Neoplasia Disorders. Accessed February 11, 2025. https://www.amend.org.uk/
16. Vannucci L, Marini F, Giusti F, Ciuffi S, Tonelli F, Brandi ML. MEN1 in children and adolescents: Data from patients of a regional referral center for hereditary endocrine tumors. Endocrine. 2018;59(2):438-48. PMID: 28530019 DOI: 10.1007/s12020-017-1322-5
17. Falchetti A. Genetic screening for multiple endocrine neoplasia syndrome type 1 (MEN-1): When and how. F1000 Med Rep. 2010;2:14. PMID: 20948872 PMCID: PMC2948394 DOI: 10.3410/M2-14
18. van den Broek MFM, van Nesselrooij BPM, Pieterman CRC, et al. Clues for genetic anticipation in multiple endocrine neoplasia type 1. J Clin Endocrinol Metab. 2020;105(7):dgaa257. PMID: 32396602 DOI: 10.1210/clinem/dgaa257
19. Newey PJ, Newell-Price J. MEN1 surveillance guidelines: Time to (re)think? J Endocr Soc. 2022;6(2):bvac001. PMID: 35079671 PMCID: PMC8783614 DOI: 10.1210/jendso/bvac001
20. Hai N, Aoki N, Sjimatsu A, Mori T, Kosugi S. Clinical features of multiple endocrine neoplasia type 1 (MEN1) phenocopy without germline MEN1 gene mutations: Analysis of 20 Japanese sporadic cases with MEN1. Clin Endocrinol (Oxf). 2000;52(4):509-18. PMID: 10762295 DOI: 10.1046/j.1365-2265.2000.00966.x
21. Shah SR, Raghavan R, Desai DC, et al. An Indian family of multiple endocrine neoplasia type 1 (MEN1): Molecular diagnosis, treatment, and follow-up. Indian J Gastroenterol. 2008;27(6):242-4. PMID: 19405259
22. Giraud S, Choplin H, Teh BT, et al. A large multiple endocrine neoplasia type 1 family with clinical expression suggestive of anticipation. J Clin Endocrinol Metab. 1997;82(10):3487-92. PMID: 9329390 DOI: 10.1210/jcem.82.10.4052
23. Thompson M, Hogg P, De Paoli A, Burgess J. Parental multiple endocrine neoplasia type 1 (MEN1) is associated with increased offspring childhood mortality. J Clin Endocrinol Metab. 2019;105(4):dgz231. PMID: 31781766 DOI: 10.1210/clinem/dgz231
24. van Alewijk L, Davidse K, Pellikaan K, et al. Transition readiness among adolescents with rare endocrine conditions. Endocr Connect. 2021;10(4):432-46. PMID: 33764888 PMCID: PMC8111322 DOI: 10.1530/EC-20-0304
25. Brandi ML, Agarwal SK, Perrier ND, Lines KE, Valk GD, Thakker RV. Multiple endocrine neoplasia type 1: Latest insights. Endocr Rev. 2020;42(2):133-70. PMID: 33249439 PMCID: PMC7958143 DOI: 10.1210/endrev/bnaa031
26. Diaz-Soto G, Linglart A, Sénat MV, Kamenicky P, Chanson P. Primary hyperparathyroidism in pregnancy. Endocrine. 2013;44(3): 591-7. PMID: 23670708 DOI: 10.1007/s12020-013-9980-4
27. Pieterman CRC, Schreinemakers JMJ, Koppeschaar HPF, et al. Multiple endocrine neoplasia type 1 (MEN1): its manifestations and effect of genetic screening on clinical outcome. Clin Endocrinol (Oxf). 2009;70(4):575-81. PMID: 18616711 DOI: 10.1111/j.1365-2265.2008.03324.x