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# Multiple endocrine neoplasia type 1 caused by mosaic mutation: what about clinical follow up and genetic counseling?

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60 **Abstract (136/250):**

61 MEN1 is an autosomal dominant hereditary syndrome characterized by several endocrine  
62 tumors, in most cases affecting the parathyroid glands, pancreas, and anterior pituitary. It is  
63 the result of inactivating mutations in the tumor suppressor gene *MEN1*. More than 1300  
64 different mutations have been identified in this gene. Mosaic *MEN1* mutations have been  
65 previously described in only a few patients in the literature. In this paper we provide a review  
66 of six cases of *MEN1* mosaicism reported in the literature supplemented with six additional  
67 cases described by the French TENgen network of laboratories. This review highlights that (i)  
68 *MEN1* mosaicism is not associated with a mild phenotype, (ii) results in the same natural  
69 history as heterozygous *MEN1* mutation, and (iii) that more systematic detection of *MEN1*  
70 mosaic mutation enables improvements in both patient monitoring and genetic counseling.

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**MAIN TEXT**

74 **BACKGROUND**

75 Multiple endocrine neoplasia type 1 (MEN1) is a rare disease caused by inactivating  
76 mutations in the *MEN1* gene (1). MEN1 is characterized by a broad spectrum of clinical  
77 manifestations from which the three cardinal lesions are primary hyperparathyroidism (PHPT),  
78 pituitary neuroendocrine tumors (PitNETs), and neuroendocrine duodeno-pancreatic  
79 tumors (2). Other neuro-endocrine tumors (NETs) such as adrenal cortical tumors,  
80 bronchopulmonary NETs, or thymic NETs may also be associated. Twenty-eight to 70% of

81 MEN1 patients die due to the disease, particularly due to the pancreatic and carcinoid lesions  
82 (3). In 2012 a group of experts provided guidelines for the evaluation, treatment, and genetic  
83 testing of MEN1 disease (4). MEN1 is diagnosed based on clinical criteria in all patients with  
84 two or more MEN1-related tumors, on family criteria in patients having one MEN1-related  
85 tumor and a first-degree relative with MEN1, and on genetic criteria in all patients,  
86 symptomatic or not, who carry a *MEN1* pathogenic variant. The MEN1 diagnosis allows  
87 patients to benefit from a multidisciplinary follow-up program which enables early detection  
88 and treatment of lesions (4, 5).

89 *MEN1* is a tumor suppressor gene (1, 6) and *MEN1* pathogenic or likely pathogenic  
90 variants are detected in 90% to 95% of family cases, and in 30-45% of sporadic cases bearing  
91 the classical triad (7, 8, 9). A false-negative genetic test can occur in cases where a *de novo*  
92 mutation occurs during postzygotic development, that is, after fertilization. In these cases,  
93 only a proportion of cells in the organism harbor the variation; a feature termed mosaicism or  
94 somatic mosaicism. In mosaicism, germline genetic testing may be negative if the fraction of  
95 mutated alleles in the blood is below the detection threshold. Only a few cases of *MEN1*  
96 mosaicism have been reported in the literature (10, 11, 12, 13, 14). The impact of *MEN1*  
97 mosaicism on patient phenotype and on the natural history of the disease is unknown. Here  
98 we review all published cases of mosaicism and additionally consider six unpublished cases  
99 from the TENgen group (French network of laboratories working on NETs), in order to clarify  
100 the clinical presentation and natural history of *MEN1* mosaicism and then discuss appropriate  
101 genetic counseling.

102

103 REPORT

104 To date, only 6 cases of *MEN1* mosaicism have been reported in the literature (see  
105 Table). The first description was published by Klein *et al* in 2005 (10) who used molecular  
106 subcloning to identify a *MEN1* truncating mutation with a 10 % allele frequency in a 27 year-  
107 old woman who presented all typical *MEN1* lesions (PHPT, prolactinoma, and a pancreatic  
108 lesion, patient #1). The second case (patient #2), a woman diagnosed with PHPT at age 52,  
109 was reported by Farook *et al* in 2011(11). She presented several recurrences of PHPT and her  
110 daughter also developed PHPT, leading to genetic testing. The index case later developed a  
111 pituitary microadenoma and two pancreatic lesions. A mosaic mutation in *MEN1* was  
112 identified at a level of 10% and the same mutation found in her daughter at the heterozygous  
113 level. Mauchlen *et al* also reported a case of *MEN1* mosaicism with 15 % of mutated alleles in  
114 a 43-year-old patient with a parathyroid adenoma and pancreatic gastrinoma (patient #3)  
115 (12).

116 The three other cases were reported in relatively older patients. Two were identified  
117 by Coppin *et al* (13) using NGS. The first was a patient who developed PHPT at age 57 and a  
118 pancreatic NET at age 66 (patient #4). The mutation (6 % mutated alleles) had previously been  
119 identified at the heterozygous level in her daughter. The second case was a 68-year-old  
120 patient with hyperparathyroidism and a PitNET (patient #5) with 15 % mutated alleles. Later  
121 Beijers *et al* described an entire *MEN1* gene mosaic deletion, using MLPA, in a 63-year-old  
122 patient with PHPT and metastatic pancreatic NETs (patient #6, 14). Again, the deletion had  
123 previously been identified at a heterozygous level in his 2 children.

124 In addition to cases from the literature review, we present here 6 new cases of *MEN1*  
125 mosaicism identified by next-generation sequencing (NGS) during recent years in the French  
126 TENgen network. Three were identified in young patients. The first showed a severe clinical  
127 presentation: the patient developed PHPT at age 28, an endocrine thymic tumor at age 35 and

128 a pituitary adenoma at age 37 (patient #7). The proportion of mutated alleles was 6%. The  
129 second case was a 24-year-old man harboring a *MEN1* mosaic mutation at a level of 10 %  
130 (patient #8). He presented with PHPT and a duodenopancreatic NET and developed a PitNET  
131 at age 27. In the third case, a *MEN1* mosaic mutation was found in a 24-year-old man at a level  
132 of 11 % with a milder clinical presentation, only a PitNET being diagnosed (patient #9).

133 Another *MEN1* mosaic mutation was identified in an older woman first reported in  
134 2013 by Cuny et al (15) who developed PHPT and a PitNET before age 45. Her daughter was  
135 diagnosed with a heterozygous frameshift insertion of 26 nucleotides in *MEN1*, discovered  
136 after she developed a macroprolactinoma at age 13 and PHPT at age 20. Using NGS we  
137 retrospectively identified the same truncating mutation as in her child, at a level of 6.3 %  
138 mutated alleles (patient #10).

139 We also detected *MEN1* mosaicism in two older patients with severe MEN1. The first  
140 patient presented with PHPT, a PitNET and duodenopancreatic NETs at age 46 and an  
141 endocrine thymic tumor was diagnosed a year later (patient #11). The proportion of mutated  
142 alleles identified by NGS was 2.5%. Additionally, *MEN1* mosaicism was identified at 9.4% in a  
143 patient who presented at age 43 with PHPT and a metastatic thymic NET. He later developed  
144 duodenopancreatic NETs at age 53 (patient #12).

145 We compared the age of occurrence of the first, second and third lesions of the classic  
146 MEN1 triad (PHPT , PitNET, and duodeno-pancreatic NET) between these 12 patients with  
147 *MEN1* mosaicism and the 497 index cases with pathogenic and likely pathogenic variants from  
148 the UMD-MEN1 database as previously described (16). No difference in the cumulative  
149 incidence of lesions was found (Figure 1).

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153 DISCUSSION

154           Only six cases of *MEN1* mosaicism have been reported in the literature to date (10, 11,  
155 12, 13, 14). We report here six new patients, thus constituting the largest series ever reported.  
156 Some studies have suggested that the *MEN1* phenotype may be attenuated in patients with  
157 *MEN1* mosaicism (11). This review clearly demonstrates that patients with *MEN1* mosaicism  
158 can develop the classical triad (patients #1, #3, #4), even early in life (patients #1, #4). Patients  
159 with *MEN1* mosaicism appear to develop the classic *MEN1* lesions at the same age as others  
160 (Figure 1). Moreover *MEN1* can become a very aggressive disease with multiple lesions (6  
161 patients reported here showed at least 3 *MEN1* lesions) or show metastatic lesions (patients  
162 #6, #12) even in patients harboring *MEN1* mosaicism. For this reason careful monitoring in  
163 these patients must not be relaxed.

164           In terms of the nature of the variant, we observed that all types of alterations were  
165 represented in patients with mosaicism (5/12 frameshift variants, 3/12 non-sense variants, 2  
166 variants affecting splice junctions, 1 entire gene deletion, 1 missense variant). A relationship  
167 between mutated allele frequency and the severity of the disease was not established. In  
168 patient #11, a very low mutated allele frequency of 2.5% was responsible for disease affecting  
169 multiple tissues, whereas mosaicism at 10% can cause complete *MEN1* disease at a young age.  
170 For the moment, there is no argument in favor of modifying the follow-up program of *MEN1*  
171 patients with mosaicism in relation to either age of onset or frequency.

172           *MEN1* mosaicism can be discovered in index cases with a symptomatic child harboring  
173 a heterozygous mutation (patient #2, #4, #6, and #10). First-line negative genetic screening by  
174 Sanger sequencing could lead to the conclusion of a phenocopy in the symptomatic parent  
175 and the exclusion of other siblings from presymptomatic genetic screening. We suggest that



176 physicians should consider that a symptomatic parent with a child presenting with an  
177 apparently *de novo* mutation may harbor a mosaic mutation until proven otherwise. We note  
178 that in the literature there is only one symptomatic parent of a child carrying a *MEN1*  
179 mutation, in whom genetic explorations were negative, even by deep NGS (17). This man  
180 presented with hypercalcemia and elevated PTH levels (10.9 mg/mL, 80 pg/mL (normal assay  
181 range 14–72)) at age 63, but imaging data (ultrasound and Sestamibi parathyroid scan)  
182 provided no information. The analysis of abnormal tissue in this case could have made it  
183 possible to definitively exclude mosaicism.

184 *MEN1* mosaicism can also be identified in sporadic index cases bearing one or several  
185 *MEN1* lesions. Success in identifying *MEN1* mosaicism in these patients is really fortunate for  
186 the patient and his/her family. Firstly, it allows confirmation of the *MEN1* diagnosis in the  
187 patient, even in a patient with an isolated PitNET (patient #9), or late multiple lesions (patient  
188 #5). Additionally it clarifies genetic counseling. Since the disease is a mosaic, it confirms the  
189 appearance of the disease in the patient. Consequently, the patient's parents and siblings can  
190 be reassured and excluded from a *MEN1* follow-up program. Presymptomatic genetic  
191 screening can also be started for the patient's children. In fact, the component of genetic  
192 counseling that addresses the risk of recurrence remains challenging in mosaic genetic  
193 diseases, since it depends on the proportion of germ cell progenitors that harbor the  
194 mutation. One way in which to determine this would be to genotype the sperm of male  
195 patients (18, 19). However, no study has thus far been conducted to determine the reliability  
196 of a negative result. Nevertheless, as NGS can detect mosaic variants at low AF (13, 20, 21,  
197 22, 23); we suggest geneticists and physicians keep in mind that mosaicism is likely  
198 underestimated in unresolved *MEN1* patients.

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202

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208

209 **Ethics declaration:** Informed consent was obtained from the subjects involved in the study.

210 The study was conducted according to the guidelines of the Declaration of Helsinki and the UE  
211 General Data Protection Regulation.

212

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312 Figure 1: Cumulative incidence of the first, second and third MEN1 cardinal lesions in patients  
313 with MEN1 mosaicism and in index cases from the UMD-MEN1 database.

314 A total of 497 index cases with heterozygous MEN1 (likely) pathogenic variants, and for which  
315 the age of occurrence of the lesions of the classic MEN1 triad was known were included.

316 Patients from the UMD MEN1 database with incomplete clinical data were excluded. A) Age  
317 at occurrence of the first MEN1 cardinal lesion. B) Age at occurrence of the second MEN1  
318 cardinal lesion. C) Age at occurrence of the third MEN1 cardinal lesion.

319 Log rank test performed with Prism V9 (Graphpad) showed no difference between the 2  
320 groups for the 3 conditions.

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