

*Original article - Title: **Prophylactic thyroidectomy in children with multiple endocrine neoplasia type 2***

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Abstract

Background:In patients with MEN2 syndrome genetic testing offers early diagnosis, stratifies risk of developing Medullary Thyroid Cancer (MTC) and informs timing of thyroidectomy, paradigm of Precision Medicine. Efficacy of treatment, that hinges on a timely and safe operation, tailored on specific mutation, is not known in the UK.

Methods:This study set to retrospectively review diagnostic and clinico-pathological outcomes of DNA-directed Prophylactic Thyroidectomy in children with MEN2 diagnosed and treated before the age of 16 between 1995-2013, by inviting all UK Academic Centers to participate with coded data. American Thyroid Association 2009 Guidelines (ATA2009) were used as a benchmark for adequate treatment.

Results:Seventy-nine children from sixteen Centers had total thyroidectomy: 38 (48.1%) had genetic test and 36 (45.5%) had an operation performed above the age recommended by ATA2009; pathology showed MTC in 30 (38%). There was no mortality, no significant dysphonia. Late surgery, above-normal preoperative calcitonin and MTC on pathology correlated with late DNA test. Twenty-five children had lymphadenectomy, showing higher occurrence of parathyroid excision (WMD 0.61,95%CI 0.24-0.98,p=0.001), hypocalcaemia requiring medication (OR 5.42,95%CI 1.87-15.67,p=0.002) and permanent hypoparathyroidism (OR 4.50,95%CI 1.39-14.61,p=0.01) compared to total thyroidectomy alone. Lymphadenectomy correlated with abnormal preoperative calcitonin (p=0.025). Only one MEN2B child presented positive nodes. Age did not impact on complications. At a median follow-up of 105 months 20 children (28.2%) show within-range and 24 (33.8%) above-normal calcitonin.

Conclusion: Late genetic test may preclude age-appropriate surgery, increasing risk of operating when MTC has developed. Lymphadenectomy may increase risk of postoperative hypoparathyroidism. Early genetic test and age-appropriate surgery may help avoid unnecessary lymphadenectomy and improve outcomes. (246 words).

Introduction

Precision Medicine is the new watchword for preventative and personalized treatments based on phenotypic, biomarker and genetic characteristics[1], while Surgical Precision is a popular catchphrase, which became idiom for doing something very well[2]. Both play an important part in managing patients with MEN2, an autosomal dominant hereditary cancer syndrome associated with Medullary Thyroid Cancer (MTC), which is frequently first manifestation and remains the principal MEN2 related cause of death[3]. Estimated prevalence of MEN2 (1 in 30,000) implies that in the UK there may be about 2000 patients, who will or have already developed MTC[4].

Early identification of affected children followed by prophylactic thyroidectomy is currently the only effective strategy to prevent development and spread of MTC. In the past, clinical observation with regular measurement of basal and stimulated calcitonin was the only available-if imperfect- strategy aiming at early diagnosis[4].

Establishing causative role of RET in MEN2 allowed for clear and early distinction between affected and non-affected children[5, 6]. Correlation between specific RET mutations and the onset and course of MTC enabled risk stratification based on genetic signature and led to recommendations for prophylactic thyroidectomy at the earliest stages of C-cell disease[7]. In 2009 revised American Thyroid Association (ATA) Guidelines marked a significant shift from a pure DNA-based model of planning thyroidectomy into an integrated genetic, clinical, radiological and biochemical concept[8, 9]. The modern strategy for prophylactic management of MTC in MEN2 syndrome, based on tailoring surgery to subcategories of patients with distinct risk for disease, has to be complemented by precisely timed, safe and meticulously performed surgery, as thyroidectomy in young children is known to have a higher rate of complications as compared to adults[8]. This study aims to assess how and with what results Precision Medicine, as condensed in ATA'09 guidelines, has been implemented in the management of MEN2 in the United Kingdom.

Materials and Methods

A retrospective nationwide medical record review was designed to investigate timeliness, quality and efficacy of thyroidectomy in children with MEN2. University hospitals in the UK managing patients with MEN2 were invited to identify children who had genetic test and DNA-directed thyroidectomy for MEN2 between 1995 and 2013.

Only children who were diagnosed and treated before they turned sixteen were included, as this age is a limit to be considered a child in UK.

We included cases diagnosed since 1995, as discovery of causative RET mutation in 1994[6] was a pivotal event in developing best clinical strategies[9] and UK health system was an early adopter of genetic testing. Diagnosis of MEN2 syndrome was based on detection of RET proto-oncogene mutations at multiple exons (10,11,13,14,15 and 16) or non-RET mutations that were proven to cause the syndrome[10] and confirmed on a duplicate DNA sample.

The closing year was chosen to allow for postsurgical follow-up of at least one year, as it includes the first long-term follow-up basal calcitonin sampling.

Permission for data collection from medical records of children was sought from the participating Institutions. All identification data of the children were removed from the medical records prior to data collection. Because de-identified data were used, and it was not possible to trace any of the data to the actual individual, individual patient consent was not required. Only information required for answering the research question was extracted and coded. Data in electronic format were accessible to authorized personnel only. No intervention other than recording, classifying, counting and analysing of data took place.

Each centre was visited by a research team (FPP,TE,CM), who entered anonymised data from hospital records into a research database. Information on diagnostic, clinical and pathological outcomes was systematically recorded according to a standardised protocol to ensure accuracy of collected data.

Children with a clinical diagnosis of MEN2A, MEN2B and FMTC were stratified into four ATA 2009 risk groups based on their DNA profile.

ATA 2009 guidelines were used as a benchmark for adequate management of children with MEN2

despite the fact that some of children were operated before publishing of guidelines, as such integrated genetic, clinical, radiological and biochemical management concept was prevalent long before 2009.

Measures of outcome

Preoperative basal calcitonin levels were recorded as within or above normal range, as each laboratory referred to a locally approved interval of normal values based on test sensitivity. Within abnormal results, calcitonin >40 pg/ml was identified as such level suggests nodal metastases[11].

Postoperative basal calcitonin levels were recorded as undetectable, or detectable within or above normal limits, and >40 pg/ml.

Age of children (in years) at the time of DNA test, at the time of surgery, and type of operation (total thyroidectomy, with or without lymph node dissection) were recorded and compared to recommendations per each of the risk classes defined by ATA 2009 guidelines.

When lymph node dissection was performed, we indicated whether the central or lateral neck compartments were involved, as described in operating notes and pathology report. Single lymph nodes occasionally found at pathology did not account for neck compartment dissection unless lymphadenectomy was stated in the operative note; however such single nodes were included for lymph node count and positivity analysis.

The number of parathyroids identified, preserved in situ, excised or auto-grafted was obtained.

Postoperative hypocalcaemia was defined as serum calcium level <2.2 mmol/l, without or with clinical symptoms. We recorded calcium level as sampled on the first postoperative day along with the number of patients whose status was defined as hypocalcaemic during hospital stay as of medical records.

Hypocalcaemia during hospital stay indicated that repeated blood samples showed low calcium or the patient had symptomatic hypocalcaemia. Symptomatic hypocalcaemia was further classified as requiring treatment with intravenous or oral calcium and α -calcidol during hospital admission, for less than 12 months (transient hypoparathyroidism), or \geq 12 months (permanent hypoparathyroidism).

Postoperative complications including but not limited to laryngeal nerve and parathyroid function were also recorded and classified by the Clavien-Dindo scale[12].

Pathological results were classified as normal thyroid, C-cell hyperplasia or medullary thyroid cancer

(MTC).C-cell hyperplasia (CCH) was defined by evidence of more than 50 C-cells observed in at least three low-power fields at 100x magnification or equivalent. MTC was diagnosed in case of atypia of C-cells and their nuclei in combination with spreading of C-cells through basement membrane as a sign of infiltrative C-cell proliferation[13].

Tumor size>10 mm, lymph node involvement as well as the presence of multifocality, lymphovascular invasion or extrathyroidal extension were recorded. If multiple foci of MTC were present, the largest tumour dimension was used for analysis.

The risk of finding MTC at pathology was computed against timely DNA test and timely operation, by ATA risk class and by preoperative calcitonin status.

Lymph node status was defined N0 (lymph node metastases:absent),N1 (present), or Nx (no lymph node dissection performed).

Variables were analysed using standard descriptive statistics (mean,median,SD,frequencies). The ANOVA test was used to analyse differences in mean values among multiple groups. Associations between categorical variables were evaluated with univariate analysis by X^2 test and logistic regression. Where appropriate, for dichotomous outcomes we estimated a relative risk (RR) and its 95% confidence interval (95% CI), while for continuous outcomes an estimate of treatment effect was calculated by the mean difference (MD) and 95% CI.

Differences were explored in univariate analysis between characteristics of patients (e.g. age, gender), disease (e.g. risk-level genotype, preoperative basal calcitonin level, presence of MTC), type of surgery (with or without LND) and complications.

Candidate variables for multivariate model were chosen for clinical relevance and significance on univariate analysis. Statistical significance was set at 0.05. Data were analysed using SPSS software (SPSS ver. 22.0.0, SPSS Inc.,Chicago, IL).

Results

Between January 1995 and April 2013, 79 children (36 boys) diagnosed with MEN2 on the basis of genetic test by the age of 16 were identified from 16 UK centres participating to the study.

The majority of children were found to have MEN2A and commonest RET mutation was in the codon 634 (Table 1).

Preoperative and postoperative basal calcitonin levels were determined by either immunoradiometric or chemiluminescent assays.

Preoperative basal calcitonin levels were above normal in 49 (62%) and >40 pg/ml in 16 (20.3%). Most children with >40 pg/ml basal calcitonin were in high risk groups (Table 2).

Timing of DNA test (tables 2 and 3)

Median age at genetic test was 4.29 years. Forty-one (51.9%) children had DNA test by the age recommended by ATA 2009 Guidelines. All children were asymptomatic for C-cell disease at the time of diagnosis.

The majority of children who had genetic test beyond recommended age, had above normal preoperative calcitonin levels and had already developed MTC at the time of surgery; both observations were significantly more frequent in high risks groups.

At multivariate analysis the odds of finding MTC at pathology were 7-fold higher in children with a preoperative calcitonin >40 pg/ml; the odds of finding preoperative calcitonin >40 pg/ml were decreased by 8% by having a timely DNA test, and by 1% if a child was ATA risk class A.

Median time interval between genetic test and surgery was 9.81 months, significantly longer in lower risk groups.

Timing of surgery (tables 2 and 3)

Median age of children undergoing surgery was of 6.24 years. Forty-three children (54.4%) had surgery at the appropriate age (by ATA 2009 guidelines), significantly more so in low risk groups.

At multivariate analysis surgery at recommended age was significantly dependent on a genetic test

performed by the recommended time.

The majority of children who had late surgery presented with above-normal preoperative calcitonin and MTC on histology.

Type of surgery (Table 2)

Patients were all operated by paediatric, ENT or general surgeons with expertise in endocrine surgery. Fifty-four children (68.4%) underwent total thyroidectomy (TT) alone. TT was performed more frequently in lower than higher risk groups. More than three-quarters of patients had TT alone in keeping with ATA 2009 guidelines, and children in lower risk groups were more likely to have TT as recommended, than higher risk groups. Twenty-nine children (59.2%) who had TT also had above-normal preoperative calcitonin levels.

Twenty-five children (31.6%) had TT and central compartment (Level 6) lymph node dissection (LND, or lymphadenectomy), with three of them also having lateral neck compartment dissection (level 3,4).

LND was performed more frequently in higher than lower risk groups and predominantly (80%) in patients with elevated preoperative calcitonin levels. The decision to perform LND was in keeping with ATA 2009 recommendations in 11 children (44%). Recurrent Laryngeal nerves (RLN) were seen and preserved in all cases.

Postoperative complications (Table 4)

The majority of postoperative complications were related to calcium control and were consistently more represented in patients who underwent LND as compared to TT alone.

Thirty-nine children (49.4%) had a postoperative calcium measurement below normal on the first postoperative day and this was more frequent when LND was performed. Twenty-two (27.8%) of these children had symptomatic hypocalcaemia, which required treatment with calcium and α -calcidol in the immediate postoperative period. Eighteen of them (22.8%) were still being treated for low calcium, up to 3 months after surgery, and fifteen (19%) beyond 12 months postoperatively.

Patients who underwent LND had significantly fewer parathyroids preserved in situ and were at higher

risk of parathyroid excision compared to TT alone.

There were no cases of permanent RLN dysfunction, postoperative bleeding or reoperations.

Five children developed complications not related to postoperative calcemia. Only procedures featuring LND showed complications classified Clavien-Dindo level II or above, including one case of ITU admission and intubation. Age at surgery did not correlate with postsurgical complications.

Mean length of postoperative hospital stay was 3.15 days and was significantly longer in children who had LND.

Pathology (Table 5)

The majority of children showed either C-Cell hyperplasia (CCH) or MTC. Such findings were significantly more frequent in higher risk groups. The youngest age at which CCH alone and MTC were respectively found in class C patients were 1.46 and 0.8 years, while the oldest age for normal thyroid was 2.4 years. In class B patients the youngest age for MTC was 4.27 years (codon 620).

Of all patients who had LND only one was found to have positive lymph nodes, a child with MEN2B who was diagnosed with DNA test at 9 years of age and presented for surgery at 15 years with preoperative calcitonin >40 pg/ml.

Follow-up (Table 5)

Median follow-up was 105 months (range 18-240). Postoperative calcitonin results were available on medical records for 71 children (90%); in 27 (34%) of them calcitonin was undetectable and in 44 (56%) calcitonin was detected on at least one occasion during follow up. Of these, 20 (25.3%) children had postoperative calcitonin detectable but within normal limits and 24 (30%) above normal on at least one occasion. The only child with positive lymph nodes showed postoperative calcitonin >40 pg/ml and had clinical recurrence. No significant correlation was found between postoperative calcitonin status at follow-up (undetectable, within normal limits, above normal), and type of surgery (total thyroidectomy alone or with lymphadenectomy).

Discussion

Hereditary MTC, the first manifestation of MEN2, is highly penetrable, arises from normal C-cells and progresses early in an age-dependent process to C-cell hyperplasia and then to carcinoma; carcinoma is highly malignant and is not curable unless diagnosed and treated before extrathyroidal spread[14].

Prophylactic thyroidectomy enabled by individual DNA profile and directed by guidelines built on phenotypic, biomarker and genetic characteristics is exemplary of Precision Medicine.

Precision Medicine predicates that patients get the right treatment at the right time, with minimum ill consequences and maximum efficacy[15]. Timeliness of management of children with MEN2 has two main components, timing of genetic test and timing of thyroidectomy, as only when mutations predisposing to MEN2 are identified early enough children can access prophylactic thyroidectomy.

In this study timing of DNA test was the only independent factor that anticipated whether a thyroidectomy was performed by recommended age. Half of the children had a late DNA test, two thirds of the children showed preoperative abnormal calcitonin, half of them had thyroidectomy performed beyond age recommended by ATA'09 guidelines and half presented with MTC on histology. Overall, children in high risks groups were less likely to have genetic test or surgery at recommended age, probably a consequence of the narrower interval of time from birth to a truly prophylactic procedure.

Univariate analysis showed that late DNA test, operation beyond recommended age and above-normal preoperative basal calcitonin were factors associated with higher rate of MTC found on specimen, while at multivariate analysis the only significant risk factor for MTC was calcitonin>40 pg/ml, as in other studies[16, 17]. Calcitonin>40 pg/ml was also significantly proportional to a delayed DNA test.

Although it is desirable for all children to be tested early, age at which they undergo genetic testing may be affected by clinical and social context of diagnosis.

Opportunity for early diagnosis may be lost when parents with MTC are index cases of newly identified MEN2A kindred, but they undergo genetic test to distinguish sporadic from familial disease when their children are already beyond recommended age for testing.

A window of opportunity is also often lost when children are index cases, particularly MEN2B. Fewer than 20% of MEN2B children develop mucosal neuromas, intestinal ganglioneuromatosis-related

constipation or tearless crying during the first year of life[18], and manifestations of the syndrome can be subtle and difficult to recognise[19]. All MEN2B children in this study were index cases and had a late genetic test as a consequence of a vague clinical picture.

Because genetic screening involves the dissemination of complex information, socio-ethical barriers including inadequate decision making capacity, limited access to healthcare, and cultural, religious or economic factors may interfere with disclosure of test results to family members[20] and with decision affecting children of families at risk. Up to 15% of affected families do not accept screening, and gene carriers may delay or refuse prophylactic thyroidectomy for their children[21]. There appears to be no clear guidance from professional societies on informing family members at risk when an affected relative is reluctant to do so[22]. Genetic counselors may be unavailable, and genetic issues may be poorly appreciated[23].

Adequate preventative surgery for hereditary MTC has to amalgamate technical skills with choice of the procedure appropriate to patients most likely to benefit from it, and should be performed safely and with minimal surgical invasiveness: all these objectives have been seen as premises of best surgical outcomes[24].

All children in this study were treated by total thyroidectomy, with no mortality or postoperative bleeding requiring re-operation. Recurrent laryngeal nerve was seen and preserved in all cases.

Twenty-five children underwent also lymph node dissection, which was adopted significantly more often in high risks classes, where the majority of patients presented with abnormal calcitonin.

Lymphadenectomy was in keeping with ATA '09 guidelines in 11 children only, with more than half of ATA C class patients having lymph node dissection performed outside recommendations. On the other hand, the majority of children of lower risk classes (A,B) significantly had total thyroidectomy alone appropriate to ATA recommendations, while in patients portraying above-normal preoperative calcitonin lymphadenectomy was chosen less frequently than in higher risk classes.

This suggests that in the presence of factors such as high-risk mutation and relatively advanced age of presentation (mean age 8.1 years) surgeons may be inclined to judge that a window of opportunity to cure MTC by performing thyroidectomy alone has already closed[25]. For ATA class B, assumed to

portray lower risk of lymph node metastases compared to high risk mutations, treatment instead was less aggressive, even when calcitonin status was abnormal. It has recently been shown that when MTC has appeared even lower risk classes exhibit the same metastatic potential as higher risk classes[26]. With further studies showing no lymph node metastases when preoperative basal calcitonin level is below 40pg/ml, the latest guidelines consider now adequate total thyroidectomy without central compartment dissection for basal calcitonin<40pg/ml[22]. In this study the only child who was found to have positive lymph nodes at pathology was MEN2B and showed preoperative calcitonin>40pg/ml. The present series shows that when information on disease biology is limited, personalization of treatment based on the experience of the operating surgeon may be preferred over current recommendations.

Children who had lymphadenectomy stayed in hospital significantly longer and manifested a significantly higher risk of postoperative hypocalcaemia, with one third of them developing permanent hypoparathyroidism. Age did not impact on complications, frequency and severity of which depended solely whether lymphadenectomy was performed or not. Limited experience of pediatric thyroidectomy for MEN2 may have contributed the recorded rate of hypocalcaemic patients, with 4-5 children treated over 23 years per each Center if we were to normalize 79 patients by 16 Centers. Surgical experience is a well-recognized contributor to both positive perioperative and oncological outcomes[27] in paediatric surgery[28], so discussion on whether treatment of these rare cases should take place in fewer Centers of excellence may have positive impact on outcomes of prophylactic thyroidectomy for MEN2. At a median follow-up of 105 months the only clinical recurrence occurred in the only child with MEN2B who presented with preoperative calcitonin>40 pg/ml.

Follow-up calcitonin status did not show significant correlation to total thyroidectomy alone or with lymphadenectomy. As in other studies[29] detectable but fluctuating calcitonin levels are difficult to interpret; we found them in children with MTC but also in normal thyroid or C-cell hyperplasia: this finding raises an issue of not only cancer persistence or recurrence, but also incomplete or “less than total“ thyroidectomy in benign cases.

The majority of these patients were not treated in line with ATA guidelines, yet their 8-years follow-up

doesn't show any convincing untoward oncological outcomes; however the case mix (children from multiple Centers carrying mutations of different risk spectrum who had non-homogeneous surgical approach) and the follow-up interval of this study do not allow sufficiently informed speculation over the prognostic significance of detectable levels of postoperative calcitonin. It might be necessary to follow these children for decades to understand the fate of fluctuating levels of postoperative calcitonin with respect to original mutational status[26, 29]. Accepting concept of undetectable calcitonin validating cure would suggest that nearly two thirds of children observed in this study were not cured, posing a risk of transforming them into patients again, and posing an important problem regarding the continuity of periodic follow-up controls. Organising centrally the administrative work with information collected in a systematic and comprehensive way in a registry has been seen as the way to solve the practical problems of follow-up[30].

Although this study has limitations related to retrospective collection of data over a long period of time, it is believed to be a true reflection of the management of children with MEN2 in the UK over the last 23 years.

Findings suggest that performing genetic testing as early as possible could increase the rate of truly prophylactic thyroidectomy in children with MEN2. Research is needed to understand patients' preferences, opinions of healthcare professionals and parents' acceptance of genetic testing. Age-appropriate thyroidectomy and improved knowledge of disease behaviour in relation to mutation and calcitonin status may improve Surgical Precision by affording patients the least invasive procedure that is adequate for prevention and cure. Lymphadenectomy but not operating on younger children has shown a high rate of hypoparathyroidism, therefore lymphadenectomy should not be performed when it is not supported by the current guidelines. Our findings should encourage rethinking of how these children are treated. This study supports efforts at creating a centralized MEN2 registry, treatment of children with MEN2 into fewer Centers and discussion over the barriers of implementation of existing guidelines to promote the choice of correct surgical approach for prevention and cure.

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