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Hyperthyroidism-Related Epithelial Hyperplasia as a Potential Pitfall of Thyroid Cytology: Institutional Cytomorphological Analysis of Histologically Verified Cases

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Keywords
Thyroid gland · Hyperthyroidism-related epithelial hyperplasia · Fine-needle aspiration · The Bethesda System for Reporting Thyroid Gland Cytopathology

Abstract

Introduction: Hyperthyroidism-related epithelial hyperplasia is seldomly listed as a pitfall in thyroid cytology. Therefore, we focused on the cytomorphological characteristics of epithelial hyperplasia and compared these features with papillary thyroid carcinoma (PTC). ***Methods:*** Study group consisted of 76 patients (133 FNA specimens) histologically diagnosed with hyperthyroidism-related epithelial hyperplasia without a concomitant malignancy. The control group contained 21 histologically verified FNAs of PTCs. A total of 48 cytomorphological features were quantitatively evaluated. ***Results:*** Statistically significant differences between the study groups were discovered on the architectural, cellular, and nuclear levels. Nuclear features varied most: nuclear elongation, grooves, irregular nuclear membrane, pseudoinclusions, the presence of nucleoli or small eccentric nucleoli were clearly more common in PTC group. ***Conclusion:*** Fine-needle aspiration referrals with clinical data and thyroid function test results can facilitate the interpretation of cytomorphological features and reduce the use of undetermined categories in cases of hyperthyroidism-related epithelial hyperplasia.

Introduction

In an ideal world, benign thyroid entities would be distinguishable from neoplastic lesions in fine-needle aspirations (FNAs). However, in real life, various benign lesions imitate the nuclear, cellular, and architectural cytomorphological features of neoplasms. The overlap of cytomorphological features between benign

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and malignant thyroid lesions has been profoundly studied and reviewed. A plethora of benign entities can cause diagnostic challenges, namely, cystically degenerated, inflammatory, and follicular-patterned lesions [1–3]. Both qualitative and quantitative features should be considered when interpreting cytomorphologic features [1]. Nevertheless, the interobserver variability in thyroid cytology is far from perfect, especially in indeterminate categories where it is as low as $\kappa = 0.11$ compared to $\kappa = 0.61$ in the malignant category [4].

Hyperthyroidism-related cytomorphological features have been studied to a lesser extent. Hyperthyroidism can be defined as increased thyroid hormone synthesis and secretion from the thyroid gland. It can be caused by toxic nodules or tumors, autoimmune disorders, such as Graves' disease and thyroiditis, iodine-induced and drug-induced thyroid dysfunction, and the factitious ingestion of excess thyroid hormones [5]. Morphologically changes are presented as epithelial hyperplasia. Seminal works in the 1970s noted marginal vacuoles on Giemsa-based staining that represent the endoplasmic reticulum [6, 7]. Graves' disease is characterized by loosely cohesive groups and monolayered sheets formed by follicular cells with vesicular, often enlarged nuclei and prominent nucleoli [6, 8–10]. Flame cells with marginal cytoplasmic vacuoles and frayed edges are not pathognomonic, despite marginal vacuoles being associated with epithelial hyperplasia in 79% of cases in an Indian study [11]. Occasionally, focal chromatin clearing and intranuclear grooves are found [6, 8–10].

Despite being focally present, hyperthyroidism-related nuclear atypia can imitate the cytomorphology of papillary thyroid carcinoma (PTC). In studies on misinterpretations of thyroid diagnostics, degenerative and inflammation-related atypia were the most common problems in the overinterpretation of benign disorders as PTC [12–14]. Atypia may lead to false-positive results that constitute case-related interpretation errors caused by insufficient referral information. Nevertheless, the issue is more complicated: Graves' disease may contain nodules that can represent PTC. PTCs arising in Graves' disease have been studied to reveal that the application of strict diagnostic criteria, namely, nuclear elongation, intranuclear grooves, pale powdery chromatin, and small eccentric nuclei, overcomes this diagnostic challenge [10]. Currently, laboratory tests are superior for obtaining a hyperthyroidism diagnosis. However, a knowledge of cytomorphological pitfalls regarding hyperthyroidism-related epithelial hyperplasia can reduce surgical treatment in false-positive cases.

In the present study cohort, we retrospectively analyzed 133 samples of histologically proven epithelial hyperplasia cases to assess the potential for false-positive results in cases without concomitant malignancies. Different background, architectural, cellular, and nuclear features were assessed in histologically confirmed epithelial hyperplasia and PTC cases to gain data on the features that cause major misinterpretation problems.

Methods

Study Cohort

This study evaluated 154 FNAs from 97 patients. The decision on FNA procedure was made by a radiologist based on ultrasound findings, nodule size, laboratory findings, and family history. No TIRADS was applied. All FNAs were performed with ultrasound guidance. No rapid on-site evaluation was performed. Data were collected from the Pathology Laboratory Information System, Fimlab Laboratories, based on the histological diagnoses collected over a 10-year period (2010–2019). All included cases were operated on. The samples were divided into two groups according to histologically verified diagnoses. All cytological samples taken before the surgical resection of the thyroid gland were re-examined. The study group included 76 patients with histologically verified hyperthyroidism-related epithelial hyperplasia who had 133 preceding thyroid FNAs. Most of the cases were histologically diagnosed with thyroid follicular nodular disease, but three with thyroiditis and three with hyperthyroidism-related epithelial hyperplasia only. The control group comprised 21 patients with 21 FNAs preceding the surgical resection of PTC. In total, there were 97 patients with a mean age of 55.1 years (SD 15.9). The male-to-female ratio was 0.213, which included those with epithelial hyperplasia (mean age 54.6 years [SD 14.6], M:F 0.134) and those with PTC (control group, mean age 57.1 years [SD 20.3], M:F 0.615).

Cytomorphological Analysis

The samples were examined under a light microscope. The characteristics of the samples were analyzed at four levels: background, architectural, cellular, and nuclear levels. The analyzed features are illustrated in Table 1. Originally, the presence of each feature was evaluated on a scale of 0–3 (0 absent, 1 mild, 2 moderate, 3 severe) from each sample. However, the final analysis and results are based on a scale of 0–1 (absent–present). Three-level

Table 1. Cytomorphological features examined on thyroid fine-needle aspiration biopsies

Background features	**Architectural features**
Amount of colloid	Diffuse hypercellularity
Amyloid	Large intact cellular fragments
Necrosis	Sheets
Hemorrhage	Honeycombed sheets
Inflammatory background	Formation of trabeculae
Cystic	Papillary
Macrophages	Follicular
Lymphocytes	Monotony of the cell population
Plasma cells	Dyscohesive
Neutrophils	Two cell populations
Other inflammatory cells	Small groups
Cellular features	**Nuclear features**
Columnar cells	Nuclear enlargement
Cuboidal cells	Nuclear size variability
Oncocytic cells (Hurthle cells)	Nuclear hyperchromasia
Oncocytoid cells	Nuclear crowding
Squamous cell metaplasia	Nuclear elongation
Cyst-lining cells	Nuclear grooves
Giant cells	Irregular nuclear membrane
Flame cells (fire-flare cells)	Nuclear pseudoinclusions
Cell size variability	Pale powdery chromatin
Cytoplasmic granules	Presence of nucleoli
Cytoplasmic vacuoles	Oval nucleus
	Presence of small eccentric nucleoli
	Nuclear atypia
	Mitosis
	Apoptotic bodies

rating was converted to binary rating by remaining the category 0 (absent) and moving categories 1 (mild), 2 (moderate), and 3 (severe) to category 1 (present).

Statistical Analysis

Statistical analyses were performed with SPSS (version 22, IBM, Armonk, NY, USA). The data were analyzed using Pearson's chi-square test and Fischer's exact test. Differences were considered statistically significant, with a p value <0.05.

Results

Macroscopic Features

Macroscopically, most cases featured one nodule: 46 (61%) hyperthyroidism-related epithelial hyperplasia cases vs. 15 (71%) PTC cases ($p < 0.001$; Table 2).

Cytomorphological Features

Statistically significant differences between the study groups were discovered on the architectural, cellular, and nuclear levels. Overall, PTC cases demonstrated more pronounced cytomorphological changes. Table 3 reveals how different features with statistical significance were distributed between the groups.

Even though 20 features were present in the PTC group with statistical significance, four were present in about half (48–56%) of the epithelial hyperplasia cases. The features that most varied between the groups were found at the nuclear level: nuclear enlargement, nuclear size variability, nuclear elongation, nuclear grooves, irregular nuclear membrane, nuclear pseudoinclusion, the presence of nucleoli, the presence of small, eccentric nucleoli, and nuclear atypia with $p < 0.001$ (Table 3; Fig. 1).

Table 2. Nodularity vs. diffuse enlargement in studied cases

	Hyperthyroidism-related epithelial hyperplasia, *n*	Papillary thyroid carcinoma, *n*	*p* value
One nodule	46	15	**0.017**
Multinodular	30	3	0.277
Diffuse enlargement	15	1	0.313
Other/n.d.	18	2	0.527

n.d., not determined.

Table 3. Summary of cytomorphological features that were statistically significantly different between hyperthyroidism-related epithelial hyperplasia and papillary thyroid cases

Features	Hyperthyroidism-related epithelial hyperplasia group, %	Papillary thyroid carcinoma group, %	*p* value
Architectural			
Diffuse hypercellularity	29	60	0.019
Large intact cellular fragments	13	36	0.013
Sheets	33	60	0.013
Formation of trabeculae	13	36	0.016
Formation of papillae	6	52	<0.001
Dyscohesivity	8	24	0.026
Cellular			
Presence of cuboidal cells	75	96	0.023
Nuclear			
Nuclear enlargement	49	96	<0.001
Nuclear size variability	49	92	<0.001
Nuclear hyperchromasia	48	84	0.003
Nuclear crowding	56	80	0.027
Nuclear elongation	9	36	<0.001
Nuclear grooves	12	80	<0.001
Irregular nuclear membrane	21	76	<0.001
Nuclear pseudoinclusions	6	84	<0.001
Pale powdery chromatin	15	40	0.009
Presence of nucleoli	28	88	<0.001
Oval nucleus	1	16	0.002
Presence of small eccentric nucleoli	2	52	<0.001
Nuclear atypia	39	88	<0.001

On the cellular level, the presence of cuboidal cells was the only feature that displayed a statistically significant distinction between the groups. Cuboidal cells were more abundant in the PTC group (96%). Nonetheless, 75% of the epithelial hyperplasia samples still had this feature. On the architectural level, the formation of papillae, large intact cellular fragments, and sheet formation were more common in PTC but were still present in 6–33% of epithelial hyperplasia cases (Table 3; Fig. 2). Background features did not diverge between the study groups.

Original Bethesda System for Reporting Thyroid Cytopathology Classification

Table 4 visualizes the distribution of cytological diagnoses based on the Bethesda System for Reporting Thyroid Cytopathology Classification [15]. In the epithelial hyperplasia group, 48 (40%) FNAs were classified as insufficient, with none in the PTC group ($p < 0.001$). Another 48 (40%) of the samples in the study group and two (8%) in the control group were reported as benign ($p = 0.004$). The number of samples classified as atypia of

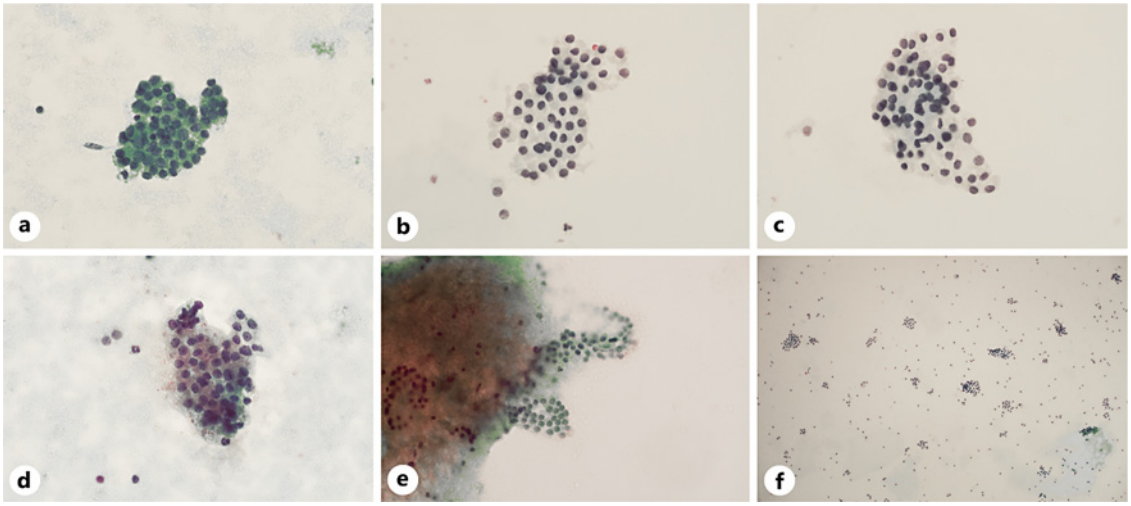

Fig. 1. Cytomorphological characteristics of cases of hyperthyroidism-related epithelial hyperplasia. **a** A group of follicular cells with crowding, irregular nuclear membranes, nuclear size and shape variabilities, and few grooves. Note the peripheral cytoplasmic vacuolization (with fire-flares better visualized in Giemsa-type stains) in epithelial hyperplasia cases. Papanicolaou stain, ×600 magnification. **b** Follicular cells with moderate size variability. The nucleoli are present. Note the peripheral cytoplasmic vacuolization (with fire-flares better visualized in Giemsa-type stains) in epithelial hyperplasia cases. Papanicolaou stain, ×600 magnification. **c** Follicular cells with moderate size variability. There is nuclear crowding focally. Note the peripheral cytoplasmic vacuolization (with fire-flare cells better visualized in Giemsa-type stains) in epithelial hyperplasia cases. Papanicolaou stain, ×600 magnification. **d** A group of follicular cells with crowding, nuclear size and shape variability, and nucleoli. Note the peripheral cytoplasmic vacuolization (fire-flare cells) in epithelial hyperplasia cases. Papanicolaou stain, ×600 magnification. **e** The formation of papillae and mild nuclear size and shape variability in an epithelial hyperplasia case. Papanicolaou stain, ×400 magnification. **f** A diffusely cellular sample with the formation of middle-sized groups and sparse follicles. Thin colloid fragment in the background. Epithelial hyperplasia case. Papanicolaou stain, ×100 magnification.

undetermined significance was 20 (17%) in the epithelial hyperplasia group and none in the PTC group (p = 0.045). Out of AUS cases there were 11 (55% of AUS cases) cases with nuclear atypia, 6 (30% of AUS cases) cases with architectural atypia, and 3 (15% of AUS cases) cases with both types of atypia. Three (2%) cases in the epithelial hyperplasia group were graded as follicular neoplasms, with none in the control group (p = 1.000). Two (2%) FNAs from the epithelial hyperplasia group and five (21%) FNAs from the PTC group (p = 0.001) were suspected to be malignant. As malignant, only PTCs were classified: 17 (71%) cases from the control group (p < 0.001).

Discussion

Hyperthyroidism-related epithelial hyperplasia, particularly hyperfunctioning nodules, may exhibit diagnostically misleading cytological features [13, 14]. It is difficult to avoid the cytologic misinterpretation of epithelial hyperplasia lesions that may cytologically mimic PTC in cases lacking the results of patients' thyroid function tests [14]. All hyperplastic and hormonally active nodules do not even cause hyperthyroidism on a biochemical level. Even when hyperthyroidism in aspirated patients is known in advance, the cytological features of thyroid lesions can lead to diagnostic pitfalls and the potential for false-positive cytological results. Hyperthyroid patients often exhibit misleading cytological atypia that can be provoked by various factors, such as antithyroid medications, radioactive iodine therapy, or the presence of concurrent thyroid conditions, such as chronic lymphocytic thyroiditis [14, 16–20]. In addition to Graves's disease, hyperthyroidism-related epithelial hyperplasia is present in thyroid follicular nodular disease, Hashimoto thyroiditis, hyperfunctioning follicular adenomas, or after lobectomy in remaining parenchyma.

Because PTC can coexist with hyperfunctioning nodules, a careful cytological evaluation only helps rule out malignancies [21]. The use of molecular and immunohistochemical methods in FNA cases with indeterminate cytology could help differentiate between benign and malignant thyroid conditions [22]. In the future, emerging artificial intelligence could be a promising technology for integrating cytomorphological

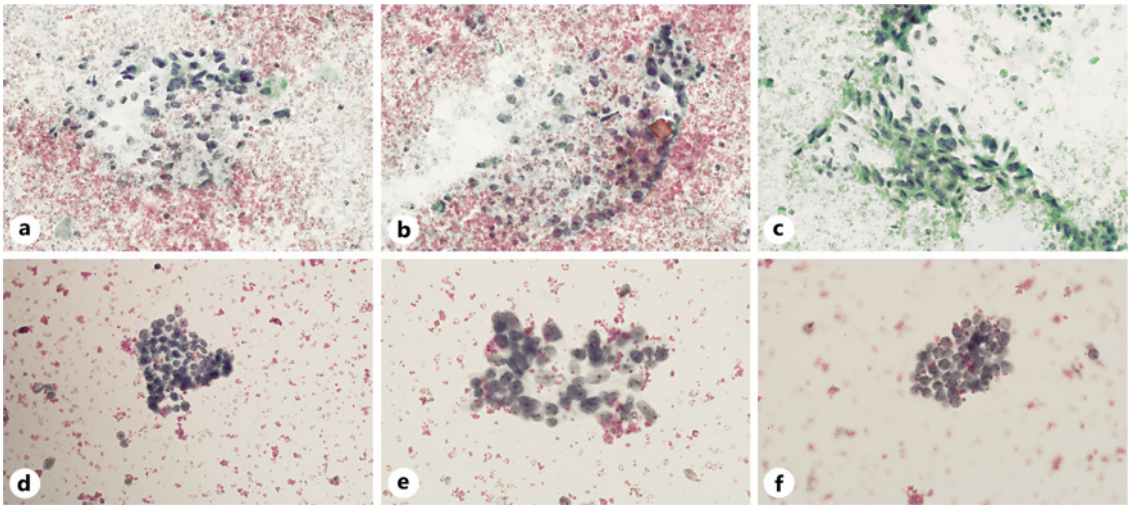

Fig. 2. Cytomorphological details of cases with cytological false-positive diagnosis suspicious for malignancy, but histological diagnosis of hyperthyroidism-related epithelial hyperplasia. **a** Nuclear pleomorphism with both round and oval to spindle nuclei and focal crowding. The background is bloody with sparse colloid fragments. Papanicolaou stain, ×400 magnification. **b** Dyscohesive epithelial cells with moderate nuclear variability and moderate hyperchromasia in bloody background. Same case as in **a**. Papanicolaou stain, ×400 magnification. **c** Spindle shaped nuclei in dyscohesive area. Same case as in **a** and **b**. Papanicolaou stain, ×400 magnification. **d** A cluster of epithelial cells with moderate nuclear variability and moderate hyperchromasia. Note some nucleoli and nuclear crowding. Papanicolaou stain, ×400 magnification. **e** Dyscohesive cells with irregular nuclear contours, nuclear enlargement and crowding. Same case as in **d**. Papanicolaou stain, ×600 magnification. **f** Fragment with nuclear crowding and nuclear enlargement and irregularity in nuclear membrane. Note nucleoli. Same case as in **d** and **e**. Papanicolaou stain, ×600 magnification.

Table 4. Cytological diagnoses' categorization based on the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC)

TBSRTC category	Hyperthyroidism-related epithelial hyperplasia group, *n* (%)	Papillary thyroid carcinoma group, *n* (%)	*p* value
Insufficient	48 (40)	0	<**0.001**
Benign	48 (40)	2 (8)	**0.004**
Atypia of undetermined significance (AUS) AUS nuclear atypia AUS architectural atypia AUS nuclear and architectural atypia	20 (17) 11 (9) 6 (5) 3 (3)	0	**0.045**
Follicular neoplasm	3 (2)	0	1
Suspicious for malignancy	2 (2)	5 (21)	**0.001**
Malignant	0	17 (71)	<**0.001**
Total	121	24	

and clinical data to reduce false-positive FNA diagnoses and indeterminate results [23, 24].

In the present study, several cytomorphological features regarding both epithelial hyperplasia and PTC were evaluated in histologically confirmed cases of epithelial hyperplasia and in a control group of PTCs. In summary, nuclear crowding, nuclear enlargement, nuclear size variability, and nuclear hyperchromasia were found in approximately half of the cases of epithelial hyperplasia. Although all were more profoundly and statistically significantly present in PTCs, the presence in the individual cases may lead to false-positive outcomes. Furthermore, the presence of cuboidal cells, sheets, and diffuse hypercellularity exhibited the highest overlap in both groups.

Hang et al. reported both nuclear and architectural atypia in non-neoplastic nodules in Graves' disease, namely, diffuse hypercellularity, large intact cellular fragments with papillae, nuclear elongation, nuclear enlargement, and nuclear crowding [9]. Another study listed the following cytomorphological features as nuclear elongation, nuclear grooves, pale powdery chromatin, and the presence of prominent eccentric nucleoli as the main cytomorphological differences when comparing epithelial hyperplasia cases with and without PTC [10]. Radioactive iodine therapy for hyperthyroidism can also lead to misinterpretation due to nuclear and cytoplasmic atypia in cytology [16, 17].

Moreover, the coexistence of Graves' disease and nodules, as well as Graves' disease and carcinoma, appears in 15% and 0.15–15% of cases, respectively [25–27]. Graves' disease can also coexist with inflammatory, degenerative, or hyperplastic disorders [28]. Epithelial hyperplasia due to various etiologies is accompanied by carcinomas in 1.6–21.1% of cases [27]. The coexistence of two or more disorders in the thyroid parenchyma is thus not unique to hyperthyroidism-related epithelial dysplasia. Inflammatory disorders may also be accompanied by epithelial changes, including dysplasia [29, 30] or even PTC [31, 32].

It is of paramount importance to have access to laboratory results or listed laboratory results in FNA referral. The FNA referral with thyroid function test results can facilitate the interpretation of cytomorphological features and reduce undetermined categories' potential use in cases in which epithelial hyperplasia causes cytomorphological atypia. In our previous study, thyroid function tests were performed in only 58% of the patients 3 months or less before FNA performance. In cases with known thyroid function laboratory results, 18% were dysthyroid, 14% were hypothyroid, and 4% were hyperthyroid. Fortunately, there was no statistically significant difference in the distribution of Bethesda categories between euthyroid and dysthyroid patients [33].

In our series, 17% of epithelial hyperplasia cases were placed in the Bethesda AUS category; overall, 21% of cases were placed in undetermined categories. Hang et al. [9] reported even higher rates in their series: 30.9% in the AUS and 39.1% in undetermined categories. Surprisingly, the Affirma gene classifier placed three cases of epithelial hyperplasia in their cohort in the suspicious category. No molecular tests were applied in the present study. Conversely, the immunohistochemical markers cytokeratin 19 and HBME-1 have been shown to play a diagnostic role in cases of PTC arising in Graves' disease [10]. Nevertheless, single markers and limited panels played lesser roles in thyroid FNA workups [34].

Poller et al. [1] elegantly summarized the issues that apply to the reduction of thyroid diagnostic errors: correlating all available clinical and imaging data, the application of ancillary techniques, in-house or external second opinions and multidisciplinary meetings, the announcement of the malignancy risk, and diagnostic uncertainty. As mentioned above, a laboratory referral with thyroid function tests is key to reducing overinterpretation. Finally, strict adherence to nuclear criteria can reduce overinterpretation [10].

Taken together, a multidisciplinary approach to the FNA evaluation of thyroid nodules is desirable, including imaging, laboratory, and clinical data. Moreover, the perceived lower risk of thyroid cancer associated with hyperfunctioning nodules cannot lead to the oversight of malignancy [35]. Therefore, the vigilance of cytologists is always necessary to correctly interpret all cytologic features.

Statement of Ethics

The Ethical Committee of the Pirkanmaa Hospital District approved the study (R15013). After approval, individual patient consents were not requested. This study was performed in agreement with the Helsinki Declaration. The need for written informed patient consent was waived by the Ethical Committee of Pirkanmaa Hospital District (decision reference number R15013).

Conflict of Interest Statement

One of authors (I.K.) was a member of the journal's Editorial Board at the time of submission. The authors have no other conflicts of interest to declare.

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Author Contributions

E.E.V. and L.V.: conceptualization, data curation, formal analysis, investigation, methodology, visualization, writing – original draft, and writing – editing; D.K.: formal analysis, methodology, resources, validation, and writing – editing; M.L.:

methodology and writing – editing; I.K.: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, validation, visualization, writing – original draft, and writing – editing. All authors have read and agreed to the submitted version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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