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Endocrine Conditions

Children are at a high risk of hypocalcaemia and hypoparathyroidism after total thyroidectomy☆

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ABSTRACT

Purpose: Disruption of calcium homeostasis is the most common complication after total thyroidectomy in adults. We explored the incidence and risk factors of hypocalcaemia and hypoparathyroidism after total thyroidectomy in children (≤18 years of age).
Methods: One hundred six children underwent total thyroidectomy. Patient, operative and outcome data were collected and analyzed.
Results: The indication for surgery was Graves' disease in 52 children (49.1%), Multiple Endocrine Neoplasia type-2 in 36 (33.9%), multinodular goiter in 3 (2.8%) and follicular/papillary thyroid carcinoma in 15 (14.2%). Neck dissection was performed in 23 children (18.9%). In 14 children (13.2%), autotransplantation was performed; in 31 (29.2%), ≥1 glands were found in the specimen. Hypocalcaemia within 24 h of thyroidectomy was observed in 63 children (59.4%) and 52 (49.3%) were discharged on supplements. Hypoparathyroidism at 6 months persisted in 23 children (21.7%). The ratios of all forms of calcium-related-morbidity were larger among children with less than four parathyroid glands remaining *in situ*: hypocalcaemia within 24 h of thyroidectomy (54.0% *versus* 47.5%; $p = 0.01$), hypoparathyroidism on discharge (64.4% *versus* 37.7%; $p = 0.004$) and long-term hypoparathyroidism (31.1% *versus* 14.8%; $p = 0.04$).
Conclusion: The incidence of postoperative hypocalcaemia and hypoparathyroidism among children undergoing total thyroidectomy is considerable. The inability to preserve the parathyroid glands *in situ* during surgery seems an important factor. For optimal outcomes, the parathyroid glands should be preserved *in situ*.
Type of Study: Prognosis Study.
Level of evidence: Level IV.

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Disruption of calcium homeostasis is the most common complication after total thyroidectomy with transient hypocalcaemia reported in over one-in-four and long-term hypoparathyroidism in up to 12% of all adult patients [1]. However, data on post-operative hypocalcaemia and hypoparathyroidism after total thyroidectomy for children is very scarce [2].

Although the cause of post-operative hypocalcaemia is probably multifactorial, the main contributing factor is parathyroid insufficiency due to damage to the functional parathyroid parenchyma. As a result of trauma, devascularisation or accidental removal of the parathyroid glands, the level of intact parathyroid hormone (PTH) in the blood decreases [3]. This can lead to transient hypocalcaemia, if the parathyroid function recovers, or long-term hypoparathyroidism, if it does not.

Identifying parathyroid glands during surgery and preserving their function can be challenging, especially in children. Failure to properly identify the parathyroid glands has been shown to be associated with an increased risk of injury to or removal of the glands [4,5] and thus subsequently with a higher risk of postoperative hypocalcaemia or long-term hypoparathyroidism. Accidental parathyroidectomy or parathyroid auto-transplantation, resulting in fewer than four parathyroid glands remaining *in situ*, has been previously shown to be fundamental in the development of post-thyroidectomy hypocalcaemia and hypoparathyroidism in adults [6,7].

The aim of the current study was to determine the incidence and risk factors of hypocalcaemia and hypoparathyroidism after total thyroidectomy in children (≤18 years of age) and particularly to evaluate whether the number of parathyroid glands remaining *in situ* was associated with these complications.

☆ Declarations of Interest: None

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1. Methods

All children who underwent total thyroidectomy between 1998 and 2018 at either University College London Hospital or Great Ormond Street Hospital (both London, United Kingdom) and were ≤18 years of age at that time were identified from our database and included in the analysis. Appropriate approval for this study was obtained.

Standard demographic (age, sex), clinical (indication for surgery), biochemical (calcium, PTH levels) and operative data (number of parathyroid glands identified during surgery, auto-transplanted or found in specimen on histology) were collected. Specifically, the PGRIS-score was calculated (*i.e.* parathyroid glands remaining in situ) using formula PGRIS = 4 − (glands auto-grafted + glands in the specimen [6]. This score represents the number of parathyroid glands remaining in their anatomical location, so excluding those glands that were accidentally removed but auto-transplanted during surgery and those which were unsuspectingly removed and sent with the pathology specimen.

Post thyroidectomy calcium related problems were recorded. These were classified as hypocalcaemia, if calcium level dropped below 2.15 mmol/L within 24 h of surgery, hypoparathyroidism on discharge, if a child required oral calcium and alfacalcidol supplementation when leaving hospital and long-term hypoparathyroidism, if supplementation was still necessary at 6 months.

1.1. Statistical analyses

Summary statistics were obtained and presented as percentages or median values. Upon comparing categorical data, the χ^2-test, or if deemed appropriate Fisher's exact test, was used, while the Mann–Whitney *U* test was used to compare continuous data. Factors associated with postoperative hypocalcaemia were examined using cross-tabs and non-parametric analyses as well as univariate analyses. Overall, a *p*-value of less than 0.05 was considered significant. All statistical analyses were performed using IBM SPSS Statistics for Macintosh, Version 23.0 (IBM Corp. IMB SPSS statistics, Armonk, NY).

2. Results

2.1. Patient characteristics

The demographic, clinical and perioperative data of the 106 children who underwent total thyroidectomy are detailed in Table 1. Overall, the majority of children were girls ($n = 68$; 64.2%), with a median age at time of surgery of 12 years [range: 0–17].

Table 1
Demographic, clinical and operative characteristics of all patients included.

Variable; *n* (%)	Number (%); $n = 106$
Patient and disease characteristics	
Sex (male)	38 (35.8)
Age (median [range]), years	12 [0–18]
Indication for surgery	
Graves' disease	52 (49.1)
Hereditary medullary thyroid carcinoma	36 (33.9)
Multinodular goiter	3 (2.8)
Thyroid carcinoma (follicular or papillary)	15 (14.2)
Perioperative variables	
Type of surgery	
Total thyroidectomy only	83 (78.3)
Total thyroidectomy plus central neck dissection	9 (5.7)
Total thyroidectomy plus central and lateral neck dissection	14 (13.2)
Number of parathyroid glands identified (median [range])	3 [0–4]
Auto-transplantation performed	14 (13.2)
Parathyroid glands remaining *in situ* (PGRIS) score	
1 *or* 2	14 (13.2)
3	31 (29.3)
4	61 (57.5)

2.2. Details of surgery

The majority of children underwent total thyroidectomy only ($n = 83$; 78.3%), while 23 children (18.9%) with Multiple Endocrine Neoplasia type 2 (MEN2) or follicular or papillary thyroid carcinoma (F/PTC) had lymphadenectomy, nine (5.7%) central and 14 (13.2%) central with lateral neck dissection.

The median number of parathyroid glands visually identified during surgery was three [range: 0–4]. In 14 children (13.2%), eight (57.1%) with Graves' disease and six (42.9%) with MEN2, auto transplantation of one or more of the parathyroid glands was performed.

2.3. Details on parathyroid glands

On final histology, one or more parathyroid glands were identified in the specimen of 31 children (29.2%). Most of these underwent surgery for MEN2 ($n = 14$; 45.2%) or Graves' disease ($n = 12$; 38.7%).

Overall, the majority of children ($n = 61$; 57.5%) had the full PGRIS score of 4, while 31 children (29.3%) had a score of 3 and 14 children (13.2%) had a score of 1 *or* 2. No differences in PGRIS-score could be found when stratifying for the indication for surgery (overall $p = 0.21$) or the extent of surgery ($p = 0.17$) (Table 2).

2.4. Postoperative outcomes

The median length of stay was 4 days [range: 1–15]. All details on calcium related complications are detailed in Table 3.

Sixty-three children (59.4%) developed hypocalcaemia within 24 h after surgery requiring a prolonged hospital stay and treatment with calcium and alfacalcidol. Among the children whose PTH was available, 37 (34.9%) had a PTH within the normal range, 41 (38.7%) had a low but detectable PTH and the PTH was undetectable in 13 children (12.3%). Fifty-two children (49.2%) were diagnosed with hypoparathyroidism on discharge and went home with oral calcium and alfacalcidol supplements. Twenty-nine (55.8%) of these children recovered within 6 months, after a median of 70 days [range: 7–150]. Long-term hypoparathyroidism, defined as dependency on oral supplementation of calcium and alfacalcidol at 6 months, occurred in 23 children (21.7%). At that time, for those in whom PTH-level was available, PTH was low but detectable in 14 children (13.2%) and remained undetectable in eight (7.5%).

Table 4 shows the occurrence of hypocalcaemia within 24 h following the operation, hypoparathyroidism on discharge and long-term hypoparathyroidism stratified by specific demographic and clinical variables. The age of the patient did not seem to be associated with the incidence of hypocalcaemia or long-term hypoparathyroidism (both $p > 0.05$). For the children' sex, no differences were observed for post-operative hypocalcaemia within 24 h of thyroidectomy or hypoparathyroidism on discharge, but the incidence of long-term hypoparathyroidism seemed to be lower among boys (boys: 10.5% *versus* girls: 27.9%; $p = 0.03$). When further exploring the characteristics of the boys and girls included, these groups were comparable regarding age at the procedure, indication for surgery, type of procedure, number of cases when auto-transplantation was performed and PGRIS-score (all $p > 0.05$).

Post-operative transient hypocalcaemia and long-term hypoparathyroidism rates were similar irrespective of the indication for surgery (all $p > 0.05$). Interestingly, however, all of the patients who developed hypocalcaemia within 24 h following surgery for either multinodular goiter (66.7%) or F/PTC (80%), were also discharged on calcium/alfacalcidol supplementation because of hypoparathyroidism on discharge. The performance of a more extensive surgery (*i.e.* addition of a central and/or lateral neck dissection to the total thyroidectomy),

Table 2
PGRIS-score stratified by indication for surgery and extent of surgery.

Variable; *n* (%)	Number (%); $n = 106$		
	PGRIS <4	PGRIS 4	*p*-Value
Indication for surgery			*0.21*
Graves' disease	20 (38.5)	32 (61.5)	
Multiple Endocrine Neoplasia type-2	20 (55.5)	16 (44.5)	
Multinodular goiter	1 (33.3)	2 (66.7)	
Thyroid carcinoma (follicular or papillary)	4 (26.7)	11 (73.3)	
Type of surgery			*0.17*
Total thyroidectomy only	39 (47.0)	44 (53.0)	
Total thyroidectomy plus central neck dissection	3 (33.3)	6 (66.7)	
Total thyroidectomy plus central and lateral neck dissection	3 (21.4)	11 (78.6)	

resulted in higher incidences of direct post-operative hypocalcaemia (82.6% *versus* 53.0%; $p = 0.01$), however the incidence for longer-term hypoparathyroidism was not influenced by this variable (both $p > 0.05$). Moreover, the performance of an auto-transplantation of one or more of the parathyroid glands did not result in significantly higher rates of any type of hypocalcaemia or hypoparathyroidism (all $p > 0.05$).

The PGRIS-score was the only variable found to be associated with the incidence of all forms of calcium-related morbidity. In general, the lower the PGRS-score, the higher the rate of hypocalcaemia. While more than four-fifth (85.7%) of children in the PGRIS-score 1 *or* 2 group developed direct postoperative hypocalcaemia, this was only 47.5% among those in whom all parathyroid glands were preserved *in situ* ($p < 0.05$). The risk for development of hypocalcaemia within 24 h after surgery was increased when the PGRIS-score was less than 4 (PGRIS-score 1 *or* 2: OR = 6.61 [95%CI: 1.37–32.11] and PGRIS-score 3: OR = 2.70 [95%CI: 1.07–6.79]; both $p < 0.05$). For the rates of hypoparathyroidism on discharge, a similar pattern was observed (PGRIS-score 1 *or* 2: 85.7% *versus* PGRIS-score 4: 37.7%; $p < 0.05$). Moreover, while for all groups the proportion of children with hypocalcaemia dropped, the rates for long-term hypoparathyroidism remained higher among those with a less than maximum PGRIS-score (PGRIS-score <4: 31.1% *versus* PGRIS-score 4: 14.8%; $p = 0.04$). Furthermore, the risk of development of long-term hypoparathyroidism was more than twofold increased among those with a PGRIS <4 (OR = 2.61 [95%CI: 1.01–6.73]; $p = 0.04$).

3. Discussion

Perhaps the most vexing complication among children and adults who undergo total thyroidectomy is immediate acute hypocalcaemia, which often becomes a long-term and sometimes a permanent problem. Understanding its incidence and risk factors, especially among children, is important, as children with long-term hypoparathyroidism, like adults, are at risk for neuromuscular symptoms, nephrocalcinosis, decreased eGFR and bone demineralisation [8–10].

Although there is considerable data on hypocalcaemia and hypoparathyroidism after total thyroidectomy among adults, reported rates of these complications vary greatly from almost zero to 12% [1,11–13]. While the reason for this wide range is probably multifactorial, one cause could be the considerable variability in the definitions and criteria used for reporting postoperative hypocalcaemia/hypoparathyroidism that currently exist [14]. In our cohort of 106 children, the incidence of hypocalcaemia within 24 h of surgery was 59.4% ($n = 63$) and because only 11 of these children (10.1%) had in-hospital recovery, a large proportion (49.3%) was discharged on calcium and alfacalcidol supplementation. This latter is comparable to rates of hypoparathyroidism in children described by other authors, although its incidence – as in adults – is very broad and ranges from one-in-four to over half of children [15–19]. Moreover, after a period of 6 months, 21.7% of our children were diagnosed with an ongoing, long-term hypoparathyroidism. We specifically do not report this as permanent hypoparathyroidism, as earlier data and our personal experience support evidence that recovery of parathyroid function in children can occur after the period of 6 months [20,21].

Overall, our data suggest that hypocalcaemia and hypoparathyroidism after total thyroidectomy are more common among children than adults. Possible explanations of this phenomena include a greater susceptibility to damage to the glands due to finer, more delicate anatomy and more challenging technical aspects of procedures inherent to pediatric surgery. When Welsh described the parathyroid glands for both children and adults in 1898, he mentioned that the parathyroid glands in children presented the same general form as in the adult but he was unclear regarding their relative size [22]. In the current study, however, we found no differences in the incidence of hypocalcaemia and hypoparathyroidism among children below and above the age of 5, indicating perhaps that finer anatomy is not an absolute risk factor. This is an important observation, as in conditions such as MEN2 there is an incentive to operate during the first few years of life and it is corroborated by our previous nation-wide study on prophylactic thyroidectomy in children with MEN2 [23]. We have also looked into whether parathyroid glands in children could be more difficult to identify because to their small size or the presence of not yet atrophied clusters of thymus tissue. In our study, the median number of parathyroid glands identified by the surgeon was three; similar as reported in adult patients [6] and thus suggesting this might not be a factor either. However, there was a discrepancy between number of glands appreciated during surgery and the final number of parathyroid glands left *in situ*, which could imply that correct visual identification of parathyroid glands in children could be more difficult.

In different analyses to establish risk factors for transient and long-term hypoparathyroidism among adults, apart from patients' age at time of surgery, the patients' sex and the extent of surgery are among the main variables [1,6,24–26]. While the incidence of hypocalcaemia within 24 h of thyroidectomy as well as transient hypoparathyroidism were similar among boys and girls; the incidence of long-term hypoparathyroidism was higher among the latter (boys: 10.5% *versus* girls: 27.9%; $p = 0.03$). Thomusch et al. [24] report a two-fold increased risk of both transient or long-term hypoparathyroidism for female sex. However, these authors state that the reason for this is unclear. The finding in the current cohort is most likely due to confounding factors and the relatively low number of boys ($n = 38$; 35.8%) included in our study. The extent of surgery, moreover, was found to be associated

Table 3
Post-operative outcomes of all patients included.

Variable; *n* (%)	Number (%); $n = 106$
Short-term outcomes	
Length of stay (median [range]), days	4 [1–15]
Levels of calcium <24 h of surgery	
Calcium <2.15 mmol/L	63 (59.4)
Hypoparathyroidism on discharge	52 (49.3)
Long-term outcomes	
Hypoparathyroidism at 6 months	23 (21.7)

Table 4
Influence of demographic and clinical variables on the prevalence of hypocalcaemia at 24 h after undergoing total thyroidectomy, on discharge from hospital and long-term hypoparathyroidism (*i.e.* >6 months).

Variable	Number ($n = 106$) (%)								
	Hypocalcaemia at 24 h			Hypoparathyroidism on discharge			Hypoparathyroidism at 6 months		
	Yes ($n = 63$)	No ($n = 43$)	*p-Value*	Yes ($n = 52$)	No ($n = 54$)	*p-Value*	Yes ($n = 23$)	No ($n = 83$)	*p-Value*
Age at time of surgery			*0.60*			*0.34*			*0.53*
<5 years	12 (66.7)	6 (33.3)		7 (38.9)	11 (61.1)		5 (27.8)	13 (72.2)	
≥5 years	51 (58.0)	37 (42.0)		45 (51.1)	43 (48.9)		18 (20.5)	70 (79.5)	*0.037*
Sex (male)	20 (52.6)	18 (47.4)	*0.31*	15 (39.5)	23 (60.5)	*0.14*	4 (10.5)	34 (89.5)	
Indication for surgery			*0.10*			*0.051*			*0.27*
Graves' disease	25 (48.1)	27 (51.9)		24 (46.2)	28 (53.8)		9 (17.4)	43 (82.7)	
Multiple Endocrine Neoplasia type-2	24 (66.7)	12 (33.3)		14 (38.9)	22 (61.1)		7 (19.4)	29 (80.6)	
Multinodular goiter	2 (66.7)	1 (33.2)		2 (66.7)	1 (33.2)		1 (33.3)	2 (66.7)	
Thyroid carcinoma (follicular or papillary)	12 (80.0)	3 (20.0)		12 (80.0)	3 (20.0)		6 (40.0)	9 (60.0)	
Type of surgery			*0.010*			*0.74*			*0.095*
Total thyroidectomy only	44 (53.0)	39 (47.0)		40 (48.2)	43 (51.8)		15 (18.1)	68 (81.9)	
Total thyroidectomy + additional neck dissection	19 (82.6)	4 (17.4)		12 (52.1)	11 (47.8)		8 (34.8)	15 (65.2)	
Auto-transplantation performed	10 (71.4)	4 (28.6)	*0.39*	8 (57.1)	6 (42.9)	*0.51*	3 (21.4)	11 (78.6)	*0.98*
Parathyroid glands remaining *in situ* (PGRIS) score			*0.010*			*0.004*			*0.015*
1 *or* 2	12 (85.7)	2 (14.3)		12 (85.7)	2 (14.3)		7 (50.0)	7 (50.0)	
3	22 (71.0)	9 (29.0)		17 (54.8)	14 (45.2)		7 (22.6)	24 (77.4)	
4	29 (47.5)	32 (52.5)		23 (37.7)	38 (62.3)		9 (14.8)	52 (85.2)	

with a higher incidence of hypocalcaemia during the first 24 h after surgery, but this association could not be found for either prolonged (*i.e.* on discharge) or long-term hypoparathyroidism. As the number of parathyroid glands remaining *in situ* [6] did not change with the extent of surgery ($p = 0.17$), the influence of the extent of surgery on the occurrence of hypocalcaemia is probably due to local trauma rather than accidental removal of any of the parathyroid glands.

The only factor found to be associated with all forms of hypocalcaemia and hypoparathyroidism after performance of total thyroidectomy in children in the current study was the number of parathyroid glands preserved *in situ*. The importance of *in situ* preservation of the parathyroid glands has been proposed most coherently by the Barcelona group as discussed by Lorente-Poch et al. [6] in their article on the influence of the number of parathyroid glands remaining *in situ* and their introduction of the PGRIS-score. In their adult cohort, the PGRIS-score correlated with all categories of post-operative parathyroid insufficiency. These results are corroborated by Luo et al. [7] who confirmed the number of parathyroid glands remaining *in situ* as an independent risk factor for hypocalcaemia, transient and protracted hypoparathyroidism. In almost half of children included in the current study (42.5%), one or more parathyroid gland was either detached from its blood supply during surgery and therefore required autotransplantation or was found in the specimen by the pathologist. This rate is substantially higher than the rates for inadvertent parathyroidectomy reported in literature for adult series, which are around 20% [27–30]. However, in most of these studies, it is unclear if the pathology report is included in their calculations. Moreover, very limited data are available on accidental removal of parathyroid glands among children. One study by Chen et al. [31] described the inadvertent parathyroidectomy rate in their cohort of 171 children. While they reported a similar proportion to that among the adult population (*i.e.* 19.4%), less than half of the children included in this study underwent total thyroidectomy, as the majority of children underwent either a hemithyroidectomy or a nodulectomy, making these statistics disparate to our cohort.

Our finding that a lower PGRIS-score was associated not only with an increased incidence of transient hypocalcaemia but also with increased occurrence of long-term hypoparathyroidism, underscores that surgical technique to preserve the parathyroid glands *in situ* is crucial for the preservation of parathyroid function and therefore calcium homeostasis. The vast majority (*i.e.* 85.6%) of children with a PGRIS-score of 1 *or* 2 developed hypocalcaemia within 24 h after surgery, all of these children had hypoparathyroidism on discharge and half of this group was suffering from hypoparathyroidism at 6 months. Children who had three parathyroid glands preserved *in situ* had better outcomes. Although 71% in that group developed hypocalcaemia directly post-surgery, they seemed to have a better ability to recover their parathyroid function, as only half of them were requiring supplementation on discharge and this proportion dropped to 22.6% at 6 months. The best outcomes were obtained when four glands were preserved *in situ*. Less than 50% of these children developed hypocalcaemia and only a little over a-third (37.7%) went home on medication. At 6 months, the hypoparathyroidism rate had dropped to 14.8%.

While the main aim is to preserve the parathyroid glands *in situ*, auto-transplantation after accidental parathyroidectomy has been described as a strategy to reduce incidence of hypoparathyroidism [7,32–34]. Skinner et al. [35] reported on a cohort of 32 children who underwent total thyroidectomy and parathyroid auto-transplantation. These authors report a more than 90% incidence of transient hypocalcaemia and an incidence of long-term hypoparathyroidism of 6% [35]. Within our cohort, auto-transplantation was performed in 14 children (13.2%). We found no differences in the rates of hypocalcaemia or hypoparathyroidism when comparing children in whom auto-transplantation was undertaken to those in whom this was not. Thus, because *in situ* preservation of the parathyroid glands seems to be associated with better outcomes, auto-transplantation should only be performed in cases of unintentional parathyroidectomy noticed during operation, not as routine technique aiming to diminish rates of hypoparathyroidism.

The current study has several limitations. Although it has one of the largest numbers of children in whom specific attention is drawn to the incidence of hypocalcaemia, hypoparathyroidism and accidental parathyroidectomy, the included number of patients is still low. While this does stress the highly selected nature of the cohort of children who undergo this type of surgery, it has statistical disadvantages. Due to the small sample size, our study has limited statistical power and statistical inferences were therefore also restricted, while the performance of subanalyses was not possible. Moreover, like all retrospective studies, selection bias may also have influenced certain variables measured.

4. Conclusion

In conclusion, the findings of our study suggest that the incidence of postoperative hypocalcaemia and hypoparathyroidism among children undergoing total thyroidectomy is higher than for adults but does not

seem to be linked to age, indication for surgery and extent of surgery. The inability to preserve the parathyroid glands *in situ* during surgery seems to be the most important risk factor for disruption of the calcium homeostasis. For optimal outcomes, we recommend that the parathyroid glands should be preserved *in situ* and auto-transplantation should be employed only in cases when accidental removal or devascularization of parathyroid glands is noticed during surgery.

5. Recommendation

Based on available data [6,36,37] and on our experience, we believe that to identify the parathyroid glans in children, these should only be sought in their orthotopic location and that no effort to identify parathyroid glands in any other position should be undertaken. Moreover, when a parathyroid gland's location necessitates mobilization in order to not remove it, we advise that this be done with minimal use of electrocautery and while trying to maintain the blood supply to that parathyroid gland. Furthermore, in our opinion the admission of calcium supplements should not be done routinely, as this might negatively impact the PTH production [38] and have other implications. Therefore, all children at our institution undergo a blood test to measure their adjusted calcium levels and levels of PTH within 24 h after surgery. Hypocalcaemia is then treated based on these outcomes and patient reported symptoms by calcium supplements as well as alfacalcidol for those in whom the PTH levels are low or unmeasurable. Regular outpatient checks are undertaken, in order to prevent unnecessary administration of calcium supplements.

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