Prevalence of Nelson’s syndrome after bilateral adrenalectomy in patients with Cushing’s disease: a systematic review and meta-analysis

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Accepted: 18 May 2021 © The Author(s) 2021

Abstract
Purpose Bilateral adrenalectomy (BA) still plays an important role in the management of Cushing’s disease (CD). Nelson’s syndrome (NS) is a severe complication of BA, but conflicting data on its prevalence and predicting factors have been reported. The aim of this study was to determine the prevalence of NS, and identify factors associated with its development.

Data sources Systematic literature search in four databases.

Study Selection Observational studies reporting the prevalence of NS after BA in adult patients with CD.

Data extraction Data extraction and risk of bias assessment were performed by three independent investigators.

Data synthesis Thirty-six studies, with a total of 1316 CD patients treated with BA, were included for the primary outcome. Pooled prevalence of NS was 26% (95% CI 22–31%), with moderate to high heterogeneity (I² 67%, P < 0.01). The time from BA to NS varied from 2 months to 39 years. The prevalence of NS in the most recently published studies, where magnet resonance imaging was used, was 38% (95% CI 27–50%). The prevalence of treatment for NS was 21% (95% CI 18–26%). Relative risk for NS was not significantly affected by prior pituitary radiotherapy [0.9 (95% CI 0.5–1.6)] or pituitary surgery [0.6 (95% CI 0.4–1.0)].

Conclusions Every fourth patient with CD treated with BA develops NS, and every fifth patient requires pituitary-specific treatment. The risk of NS may persist for up to four decades after BA. Life-long follow-up is essential for early detection and adequate treatment of NS.

Keywords Bilateral adrenalectomy · Cushing’s disease · Corticotroph adenoma · Nelson’s syndrome

Abbreviations
CD Cushing’s disease
BA Bilateral adrenalectomy
NS Nelson’s syndrome
ACTH Adrenocorticotropic hormone
RR Relative risk
MRI Magnet resonance imaging
CT Computer tomography

Introduction
Cushing’s disease (CD) is a rare disorder associated with excess morbidity and increased mortality [1, 2]. Previously, bilateral adrenalectomy (BA) was the mainstay treatment for CD. During the last decades, however, other treatment modalities have emerged, including pituitary surgery, radiotherapy and medical treatments. Despite this, BA is still considered when other treatment options have failed to achieve remission, or when a rapid relief of hypercortisolism is necessary [3].

BA is considered to be a safe and effective treatment for CD [4], especially after the laparoscopic approach was introduced during the 1990s [5]. There are, however, significant drawbacks with BA, mainly the unavoidable
chronic adrenal insufficiency, as well as the risk for Nelson’s syndrome (NS), i.e., growth of the remaining pituitary tumor and excessive production of ACTH, that may cause optic nerve or chiasmal compression and mucocutaneous hyperpigmentation [6].

The prevalence of NS varies between studies, mainly due to a lack of consensus on the definition and diagnostic criteria for the syndrome [7, 8]. Previously published studies are also inconsistent as to whether factors such as previous radiotherapy, age at BA, gender and duration of CD, may affect the risk of developing NS. Furthermore, high ACTH concentrations after BA have been suggested as a risk factor for developing NS [9–12].

Thus, the primary aim of this systematic review and meta-analysis was to estimate the prevalence of NS after BA for CD, both the total prevalence of NS as well the prevalence of NS requiring treatment with pituitary surgery and/or radiotherapy. The secondary aim was to investigate risk factors associated with development of NS.

**Methods**

A systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [13]. The PICO process was applied for the definition of the research question and eligibility criteria for the literature search. The protocol of this review was registered in the PROSPERO database (CRD42020163918).

**Search strategy**

We searched PubMed, Embase, Cochrane Library and Web of Science on February 25th 2020, with no start date restriction, for relevant articles by using the following terms: “Cushing’s syndrome” or “Cushing’s disease” or “Hypercortisolism” or “Pituitary ACTH hypersecretion” or “corticotroph tumor” or “corticotroph tumors” or “corticotropinoma” or “corticotropinomas” or “corticotrophinoma” or “corticotrophinomas” or “ACTH pituitary adenoma” or “ACTH pituitary adenomas” or “adrenocorticotropin pituitary adenoma” or “adrenocorticotropin pituitary adenomas” AND “bilateral adrenalectomy” or “bilateral adrenalectomies” or “total adrenalectomy” or “total adrenalectomies”. A detailed description of the search strategy is given in the Supplementary. Also, references of the included studies and relevant review articles were checked manually for additional articles. A new search was performed on January 12th 2021, prior submission, to identify any new publications.

**Data collection process and data extraction**

Titles and abstracts from all identified articles were screened for eligibility and further full-text assessment by three independent investigators (EP, MP, OR). Discrepancies were resolved through discussion and consensus. Duplicate articles and studies with overlapping populations were excluded. In the latter case, the publication with the largest population, more comprehensive information on relevant clinical variables and/or lowest risk of bias was included.

Full-text assessment and data extraction were conducted independently by the same investigators as above. Data on the following predefined variables were extracted: first author, year of publication, region/hospital, study period, characteristics of the study population (number of patients, gender, follow-up, age at CD, age at BA, previous treatment with radiotherapy and/or pituitary surgery, ACTH concentrations at BA, MRI findings at CD and at BA), intervention (BA as primary or secondary treatment, remission status) and outcome (criteria for NS, number of patients with NS, age at NS, time from BA to NS, ACTH concentrations one year after BA, number of patients treated for NS, type of treatment; pituitary radiotherapy and/or pituitary surgery).

One of the studies included in the meta-analysis is our nationwide Swedish study on CD [2]. Additional clinical data, not provided in the original publication, was retrieved and used in the current analysis (Table 1).

**Risk of bias assessment**

The Newcastle–Ottawa Scale [14], modified to suit the current study, was used for assessment of risk of bias of all included studies. Three investigators (EP, MP, OR) assessed the studies independently, and any disagreements were resolved by discussion. Selection, comparability and outcome were assessed through predefined criteria. All studies that provided information on NS as outcome, and/or corticotroph tumor progression, were included, and the definition as well as the treatment of NS were recorded (Table 1 and Table S1). A clear definition of NS and
| Study                  | Country | Period          | Study population n | Women n (%) | Patients with NS n (%) | Women with NS n (%) | Patients treated for NS n (%) | Follow-up–median/mean, [range] (yr) | Time from BA to NS –mean /median, [range] (yr) | Age at BA in patients with NS–median/Mean |
|-----------------------|---------|-----------------|-------------------|-------------|------------------------|---------------------|-------------------------------|----------------------------------------|------------------------------------------|------------------------------------------|
| Moore et al. [21]     | USA     | NA 120          | 89 (74)           | 9 (8)       | 8 (89)                 | 8 (7)               | 8.0 [2.0–20.0]                | 8.0 [0.5–16.0]                        | NA                                       | NA                                       |
| Scott et al. [23]     | USA     | 1952–1976 26    | 19 (73)           | 1 (4)       | 1 (100)                | 1 (4)               | 8.0 [0.5–20.0]                | 2.0 [NA]                              | 51.0                                     | NA                                       |
| Nabarro et al. [22]   | UK      | 1954–1976 32    | NA 19 (90)        | 8 (38)      | 8 (100)                | 8 (38)              | 8.0 [1.0–20.0]                | 6.5 [1.5–12.0]                        | 29.5                                     | NA                                       |
| Cohen et al. [24]     | USA     | 1951–1976 21    | 11 (92)           | 4 (33)      | NA                     | 4 (33)              | NA                           | NA                                     | NA                                       | NA                                       |
| Jordan et al. [25]    | USA     | 1952–1969 12    | NA 13 (87)        | 3 (20)      | 1 (33)                 | NA                  | NA                           | NA                                     | NA                                       | NA                                       |
| Barnett et al. [26]   | New Zealand | 1969–1980 15  | 13 (87)           | 3 (20)      | 1 (33)                 | NA                  | NA                           | NA                                     | NA                                       | NA                                       |
| Kasperlik et al. [27] | Poland  | 1958–1982 50    | 45 (90)           | 12 (86)     | 12 (86)                | 10 (20)             | 12.0 [1.0–22.0]               | 4.8 [1.5–12.0]                        | 23.6                                     | NA                                       |
| Kelly et al. [28]     | UK      | 1960–1980 38    | NA 49 (68)        | 20 (28)     | 14 (70)                | NA                  | NA                           | NA                                     | NA                                       | NA                                       |
| Kuhn et al. [29]      | France  | 1950–1987 80    | NA 10 (13)        | NA          | 10 (13)                | 12.5 [1.0–34.0]     | 9.5 [3.0–20.0]               | NA                                     | NA                                       | NA                                       |
| Grabner et al. [30]   | Norway  | 1972–1991 26    | 20 (77)           | 7 (27)      | NA                     | 7 (27)              | 5.3 [0.6–19.1]               | NA                                     | NA                                       | NA                                       |
| McCance et al. [31]   | Northern Ireland | 1983–1993 10 | 9 (90)            | 1 (10)      | NA                     | NA                  | 3.3 [NA]                     | NA                                     | NA                                       | NA                                       |
| Zeiger et al. [32]    | USA     | 1957–1999 16    | 44 (92)           | 23 (37)     | 23 (37)                | 9.5 (3.0–30.0)      | 9.5 [3.0–20.0]               | 6.6 [1.5–13.0]                        | 26.0                                     | NA                                       |
| Misra et al. [35]     | India   | 1946–1993 38    | NA 11 (29)        | 2 (13)      | 2 (13)                 | NA                  | NA                           | NA                                     | NA                                       | NA                                       |
| Jenkins et al. [36]   | UK      | 1953–1989 44    | 33 (75)           | 10 (23)     | NA                     | 19.6 [1.0–41.6]     | 15.5 [7.0–24.0]              | 33.1                                   | NA                                       | NA                                       |
| Hofmann et al. [40]   | Germany | 1997–2004 11    | NA 1 (9)          | NA          | 1 (9)                  | NA                  | NA                           | NA                                     | NA                                       | NA                                       |
| Assié et al. [52]     | France  | 1991–2002 53    | 45 (85)           | 21 (40)     | NA                     | 10 (19)             | 4.6 [0.5–13.5]               | 2 [0.5–7]                            | NA                                       | NA                                       |
| Gil-Cardenas et al. [20] | Mexico | 1990–2005 39 | 32 (82)           | 11 (28)     | 7 (64)                 | 11 (28)             | 4.4 [1–15.7]                 | 1.3 [0.2–2.8]                        | NA                                       | NA                                       |
| Thompson et al. [41]  | USA     | 1995–2007 40    | 34 (85)           | 13 (33)     | NA                     | 7 (18)              | 5 [0.2–10.2]                 | NA                                     | NA                                       | NA                                       |
| Ding et al. [42]      | China   | 2000–2008 34    | 29 (85)           | 6 (18)      | 6 (100)                | 6 (18)              | 4 [1.2–7.7]                  | NA                                     | NA                                       | NA                                       |
| Mehta et al. [19]     | USA     | 20 (85)         | 18 (5)            | 6 (100)     | 6 (18)                 | 5.4 [0.6–12]        | 0.8 [NA]                     | NA                                     | NA                                       | NA                                       |
| Olwald et al. [43]    | Germany | 1990–2013 29    | NA 7 (24)         | NA          | 7 (24)                 | 11 [0.8–51]         | 4.3 [NA]                     | NA                                     | NA                                       | NA                                       |
| Prajapati et al. [44] | India   | 1991–2013 12    | NA 5 (42)         | 5 (42)      | NA                     | 6.7 [0.3–13]        | 2.7 [1.7–5]                  | NA                                     | NA                                       | NA                                       |
| Espinosa-de-Los-      | Mexico  | 1991–2014 10    | NA 6 (60)         | NA          | 4 (40)                 | NA                  | 2.5 [2–8.5]                  | 23                                     | NA                                       | NA                                       |
| Monteros et al. [45]  | USA     | 1956–2015 88    | 64 (73)           | 47 (53)     | 34 (72)                | 14 (16)             | NA                           | 3 [1–8]                              | 35                                       | NA                                       |
| Nankova et al. [47]   | Bulgaria | 1985–2016 36   | NA 9 (25)         | NA          | NA                     | NA                  | NA                           | NA                                     | NA                                       | NA                                       |
| Chiloiro et al. [48]  | Italy   | 2003–2017 11    | 7 (64)            | 1 (9)       | NA                     | 6 (19)              | NA                           | 6 (19)                                | NA                                       | NA                                       |
| Cohen et al. [49]     | Argentina | 1974–2011 13 | 9 (70)            | 6 (67)      | 4 (31)                 | 14 [5–30]           | 2 [0.7–3.9]                  | 31                                     | NA                                       | NA                                       |
| Nagendra et al. [50]  | India   | 2005–2018 14    | NA 6 (43)         | NA          | 4 (29)                 | NA                  | NA                           | NA                                     | NA                                       | NA                                       |
information on treatment were considered to be two of the most important components of the quality assessment. We considered the definition of NS to be clear when it included either a new visible pituitary tumor or progression of a pituitary tumor remnant following BA, alone, or in combination with high ACTH concentrations and/or hyperpigmentation. Detailed description of the criteria for the risk of bias assessment is provided in the Supplementary file. Studies with an overall score ≥ 5 (max overall grade 8) and a clear definition of NS, were considered to have a low risk of bias.

**Data synthesis and statistical analysis**

Primary endpoints were the prevalence of NS, as well as the prevalence of pituitary-specific treatment for NS. Descriptive data are presented as median (range or interquartile range; IQR). Meta-analysis was performed by using the meta package in R (version 4.0.3) [15]. Statistical pooling was performed according to random-effects model due to the clinical heterogeneity among the included studies [16]. For all analyses, indices of heterogeneity, $I^2$ statistics and Cochran’s Q test, are reported. For the primary outcomes we estimated pooled prevalence with 95% confidence intervals (95% CI). Statistical significance was defined as $P < 0.05$. The possibility of publication bias was assessed by visual inspection of funnel plots as well as with the Egger’s test [17].

Sensitivity analyses were performed by excluding studies with an overall risk of bias < 5, and studies where information on diagnostic criteria for NS was lacking. By choosing the overall risk of bias < 5, all studies without adequate follow-up were also excluded (Table S2). Also, another sensitivity analysis was performed by including all studies reporting the number of patients with NS who received treatment for NS (Table 1).

Subgroup analyses were performed to investigate factors that may affect the prevalence of NS, namely pituitary radiotherapy prior to BA, prophylactic pituitary radiotherapy, overall radiotherapy (prior to BA or prophylactic), pituitary surgery (transcranial or transphenoidal surgery) prior to BA, and BA as primary or secondary treatment. For these outcomes, we estimated relative risks (RRs), or pooled prevalence, with 95% CIs. Also, in a subgroup analysis, the prevalence (with 95% CI) of NS and treatment for NS were estimated in studies where MRI was used at diagnosis and during follow-up.

Uni- and bivariate meta-regression was used to investigate whether the prevalence of NS was influenced by median follow-up time or age at BA. The meta-analysis was performed by using the Metareg command in R. The estimated association is reported as β coefficient.
**Role of funding source**

The funding source had no role in the design and conduction of the study; i.e., collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

**Results**

**Identification and description of included studies**

After removal of duplicates, 1702 articles were identified (Fig. 1). Three additional articles were found after checking the reference lists of identified articles and review papers. After reviewing titles, abstracts and full-text articles, 48 articles were considered eligible for further analysis. Of these, however, 11 articles were excluded due to overlapping or identical patient cohorts. Thus, 37 studies published between 1976 and 2020, were included in the current meta-analysis (Fig. 1). All studies had a retrospective observational design. Characteristics of the included studies are presented in Table 1. Two of the included studies had an overlapping cohort where one was used for the main outcome [18] and one [19] for the subgroup analyses on the influence of radiotherapy on the development of NS. An overview of risk of bias assessment of the eligible studies is provided in Table S2.

In total, 1316 patients with CD treated with BA were included. The median follow-up after BA was 7 years (23 studies, range 3.3–22). Median age at BA in patients with NS was 31 years (13 studies, IQR 26–34). Median time from BA to the diagnosis of NS was 4 years (19 studies) with the shortest reported time being 2 months [20] and the longest 39 years [2]. At diagnosis of NS, hyperpigmentation was reported in 155 of 188 (82%) patients (19 studies) and chiasmal compression in 24 of 129 (19%) patients [11 studies].

![Fig. 1 Flowchart of study selection](image-url)
Prevalence of NS

Thirty-six of 37 studies, with total 1316 patients with CD treated with BA, were included [2, 18, 20–53]. Reported prevalence of NS ranged from 4 to 60%. The mean pooled prevalence was 26% (95% CI 22–31%) with a moderate to high heterogeneity ($I^2$ 67%, $P < 0.01$) (Fig. 2). The Egger’s test was statistically significant ($P = 0.01$), but visual inspection showed no obvious asymmetry. The significant Egger’s test indicates publication bias, probably explained by the fact that case reports and cohorts with fewer than 10 participants were excluded (Fig. S1).

In a sensitivity analysis, excluding all studies with high risk of bias (overall score < 5) and no clear definition of NS, the pooled prevalence was 31% (95% CI 24–38%; $I^2$ 76%, 17 studies, 822 patients; $P < 0.01$) (Fig. S2). In a subgroup analysis, the prevalence of NS in studies where MRI was used at diagnosis and during follow-up was 38% (95% CI 27–50%; $I^2$ 71%, 7 studies, 280 patients; $P < 0.01$).

Prevalence of treated NS

The pooled prevalence of treatment for NS was 21% (95% CI 18–26%; $I^2$ 52%, $P < 0.01$) (Table 1; 29 studies with 1074 patients). Thus, the pooled prevalence was slightly lower, compared to the pooled prevalence of NS in total, as well as the heterogeneity (Fig. S3). The funnel plot showed no asymmetry and Egger’s test was not statistically significant, indicating low possibility of publication bias (Fig. S4). In a subgroup analysis, the prevalence of treated NS in studies where MRI was used at diagnosis and during follow-up was 25% (95% CI 17–35%; $I^2$ 61%, 7 studies; $P = 0.02$).

The indication for treatment was progression of the pituitary tumor in 23 out of 28 patients (82%, five studies), optic chiasmal compression in 11 out of 91 patients (12%, 11 studies), while four patients out of 14 (one study) had both these indications for treatment. Twenty-six studies provided information on treatment modalities (pituitary surgery and/or radiotherapy). Seventy-three out of 201 patients with NS (36%) were treated with pituitary surgery, 86 (43%) with radiotherapy and 41 (20%) received both treatments.

![Fig. 2 Forest plot showing individual studies and pooled prevalence of Nelson’s syndrome after bilateral adrenalectomy in patients with Cushing’s disease. *Additional data](image-url)
Radiotherapy

Nineteen studies provided information on radiotherapy prior to BA. However, nine studies had no events and no patients in one of the arms (radiotherapy or no radiotherapy) (Table S3). Thus, ten studies were eligible for further estimation, showing that the risk for NS in patients treated with radiotherapy prior to BA was comparable to the risk in patients not treated with radiotherapy (RR 0.9, 95% CI 0.5–1.6; 10 studies with 564 patients) (Fig. 4).

Thirteen studies provided information on prophylactic radiotherapy. However, only one study provided applicable data for calculating RR, thus subgroup analysis was not performed (Table S4). In that study [20], none of the seventeen patients who received prophylactic radiotherapy developed NS, while 11 of 22 patients without radiotherapy developed NS after a mean follow-up of 4.4 years (range 10–16 years).

By using studies with information on either previous or prophylactic radiotherapy (11 studies with 603 patients; Table S5), the pooled RR was 0.8 (95% CI 0.5–1.5).

Pituitary surgery prior to BA

Of 21 studies with information on pituitary surgery prior to BA (Table S6), only ten provided information for estimation of RR. A pooled RR of 0.6 (10 studies with 430 patients; 95% CI 0.4–1.0) was found (Fig. 5), indicating that the risk for developing NS was not influenced by previous pituitary surgery.

BA as primary or secondary treatment for CD

Information on whether patients with NS were treated primarily with BA or not, was provided in ten and nine studies, respectively (Fig. S5 and S6). The pooled prevalence of NS was 26% (95% CI 20–33%) for patients treated primarily with BA and 22% (95% CI 15–31%) for patients who had been treated with pituitary surgery and/or radiotherapy prior to BA.

ACTH concentrations one year after BA

Four studies provided information on ACTH concentrations during the first year after BA [45, 49, 52, 53]. In a
study by Assié et al. the median ACTH concentration in patients who developed NS was 301 pmol/L, compared to 79 pmol/L in patients without NS (upper range of limit; URL 13 pmol/L) [52]. The median ACTH concentration in a study by Cohen et al. was 105 pmol/L in the NS group compared to 18 pmol/L in patients without NS (P = 0.007) (URL 10 pmol/L) [49]. Also, in a study by Das et al., there was a statistically significant difference in ACTH concentrations one year after BA between patients with and without NS (110 vs 21 pmol/L respectively; P = 0.002) [53]. On the contrary, Espinosa-de-Los-Monteros et al. found no difference in ACTH concentrations between the patients with NS and those without NS [45]. Thus, three of four studies found that high ACTH concentrations one year after BA were associated with the development of NS. However, since the ACTH assays and the conditions when ACTH was collected were different in these studies (Table S7), further comparison or a meta-analysis on ACTH levels after BA was not considered feasible.

**Influence of age at BA and duration of follow-up on prevalence of NS**

In a meta-regression analysis, age at BA (β-coefficient = -0.03, P = 0.4; Fig. 6) and median duration of follow-up (β-coefficient = 0.01, P = 0.7; Fig. S7) were not associated with prevalence of NS. After adjustment for follow-up, age at BA was still not associated with prevalence of NS (β-coefficient = -0.03, P = 0.4).

**Discussion**

In this study we have for the first time evaluated the pooled prevalence of NS by using a meta-analysis on data from 36 studies, including more than 1300 patients with CD treated with BA. The overall prevalence of NS was 26% and the median time from BA to diagnosis of NS was 4 years, ranging from 0.2 to 39 years. The prevalence of patients requiring pituitary-specific treatment for NS was 21%. Furthermore, radiotherapy and pituitary surgery prior to BA, as well as age at BA, did not seem to affect the risk of developing NS.

Various definitions have been used for NS over the past decades [12]. Historically, the diagnosis was based on clinical findings related to mucocutaneous hyperpigmentation and chiasmal compression, together with signs of an enlarged sella turcica on skull radiography [6]. Since then, the diagnosis of NS in most studies has been based on (i) radiological evidence of a pituitary tumor that becomes visible, or a progression of a preexisting tumor, (ii) “high” ACTH concentrations, and (iii) hyperpigmentation [54]. In the studies with the highest prevalence of NS [45, 46], the diagnosis was based on rising ACTH concentrations and an expanding pituitary mass, where 2 mm increment in tumor size on MRI was considered to be a significant growth. On the contrary, the criteria for NS in studies with the lowest prevalence were based on hyperpigmentation, often but not always combined with a pituitary tumor responding to radiotherapy and/or a radiographic evidence of pituitary tumor on skull radiography [21, 23]. Thus, the great variance in the prevalence of NS between studies can, at least partly, be explained by the different definitions of NS. Consequently, in an expert opinion published in 2010, it was suggested that the diagnosis of NS should be based on an elevated level of ACTH >500 ng/L (110 pmol/L) in addition to rising levels of ACTH on at least three consecutive occasions and/or an expanding pituitary mass, where 2 mm increment in tumor size on MRI was considered to be a significant growth. On the contrary, the criteria for NS in studies with the lowest prevalence were based on hyperpigmentation, often but not always combined with a pituitary tumor responding to radiotherapy and/or a radiographic evidence of pituitary tumor on skull radiography [21, 23]. Thus, the great variance in the prevalence of NS between studies can, at least partly, be explained by the different definitions of NS. Consequently, in an expert opinion published in 2010, it was suggested that the diagnosis of NS should be based on an elevated level of ACTH >500 ng/L (110 pmol/L) in addition to rising levels of ACTH on at least three consecutive occasions and/or an expanding pituitary mass on MRI or CT following BA [54]. Similarly, in a recently published expert consensus recommendation, based on a systematic review, it was suggested that NS should be defined as radiological progression or new detection of a pituitary tumor on a thin-section MRI.
Furthermore, the authors recommend active surveillance with MRI three months after BA, and every 12 months for the first 3 years, and every 2–4 years thereafter, based on clinical findings. The meta-regression of the current analysis did not show an association between median follow-up time and prevalence of NS. Nevertheless, NS occurred as early as 2 months [20], and up to 39 years after BA [2], supporting that life-long surveillance after BA is necessary for patients with CD.

Active surveillance with MRI was more common in studies published during the last two decades. In fact, the use of MRI in recent studies resulted in earlier detection of a growing pituitary adenoma and, subsequently, contributed to a higher prevalence of NS. Namely, the seven studies including patients treated with BA after 1990 and using MRI reported higher prevalence of NS, both overall NS and treated NS.

Whether factors such as pituitary radiotherapy affects the risk for development of NS has been evaluated in several studies. Some studies have shown that radiotherapy prior to BA, or administrated prophylactically, can prevent or delay the development of NS [20, 39]. On the contrary, other studies have not demonstrated a protective effect of radiotherapy prior to BA [18, 37] and, moreover, one study found an association with tumor progression [46]. Nevertheless, the current meta-analysis indicates that radiotherapy prior to BA does not decrease the risk of developing NS. Neither did previous pituitary surgery affect the risk for NS.

Elevated ACTH concentrations during the first year after BA have been considered to be a strong predictor of NS [49, 52]. In fact, seven studies in the current analysis included cut-off levels for ACTH concentration, arbitrarily defined, for the diagnosis of NS [18, 25, 34, 36, 41, 45, 49]. Due to the different ACTH assays, and different conditions when
ACTH was collected, no further analysis on ACTH levels was performed. Nevertheless, four studies [45, 49, 52, 53] reported ACTH concentrations one year after BA in both patients with and without NS. Three of these studies found that high ACTH concentrations one year after BA [49, 52, 53] were associated with pituitary tumor progression. Thus, these findings support the suggestion that ACTH should be monitored following BA in patients with CD [54, 55].

The prevalence of treatment for NS (21%), and the heterogeneity index (52%), were slightly lower than in the analysis of total prevalence of NS (26%, $I^2$ 67%). The majority of the patients was treated with radiotherapy, followed by pituitary surgery and combination of pituitary surgery and radiotherapy. Today, surgical removal of the pituitary tumor is considered to be the first-line therapy of NS whereas radiotherapy is considered if surgery has failed or is not possible [12, 54, 56]. In a large multi-center study by Fountas et al., the 10-year progression-free survival rates after surgery alone, or with radiotherapy, for patients with NS was 80% and 81%, respectively [57]. In comparison, progression-free survival rate in patients who did not receive treatment was 51%. Reports on the efficacy of medical therapy for NS have shown inconsistent results [56].

**Strengths and limitations**

This is the largest systematic review, and the first meta-analysis, on NS published to date. However, some limitations have to be acknowledged. Most important are the different diagnostic methods used to detect NS, and the different definitions of the syndrome between the studies. The majority of the studies have used the combination of hyperpigmentation, high ACTH concentrations and radiological findings for the diagnosis of NS. Notwithstanding these common criteria, there were still differences in the cut-offs of ACTH levels, the use of different radiological modalities over time as well as the radiological definition of progress of pituitary tumors. Moreover, in some studies radiological findings were used solely or in combination with either hyperpigmentation and/or bitemporal hemianopsia, ACTH concentrations or response to treatment of NS. Furthermore, in several studies a clear definition of NS was not provided. Nevertheless, we consider our attempt to address the heterogeneity of the included studies, through systematic review, quality assessment, and sensitivity and subgroup analyses to be a strength.

**Conclusions**

The risk of NS after BA in patients with CD is considerable and may first become clinically evident many decades later. Thus, life-long close follow-up is necessary for an early detection of a growing pituitary tumor, and adequate treatment when needed. Although this meta-analysis did not find prior surgery or radiotherapy to be associated with risk of NS, the findings are based on a limited number of studies. Thus, in order to individualize the treatment for patients with CD, further studies are needed where these and other factors possibly associated with risk of NS are evaluated.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s11102-021-01158-z.

**Acknowledgements** We would like to thank Therese Svanberg, librarian at the Medical Library at Sahlgrenska University Hospital for her expert assistance with the literature search.

**Funding** Open access funding provided by University of Gothenburg. The study was financed by grants from the Swedish state under the agreement between the Swedish government and the county councils, the ALF-agreement (ALFGBG-593301) and a grant from the Gothenburg Society of Medicine.

**Data availability** The data generated or analyzed during this study are included in this published article or in the Supplementary file.

**Declarations**

**Conflict of interest** The authors have nothing to disclose.

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**References**

1. Papakokkinou E, Olsson DS, Chantzichristos D, Dahlqvist P, Segerstedt E, Olsson T, Petersson M, Berinder K, Bensing S, Hoybye C, Eden-Engstrom B, Burman P, Bonelli L, Follin C, Petranek D, Erfurth EM, Wahlberg J, Ekman B, Akerman AK, Schwarz E, Bryngelson IL, Johannsson G, Ragnarsson O (2020) Excess morbidity persists in patients with cushing’s disease during long-term remission: a swedish nationwide study. J Clin Endocrinol Metab 105(8):2616–2624
2. Ragnarsson O, Olsson DS, Papakokkinou E, Chantzichristos D, Dahlqvist P, Segerstedt E, Olsson T, Petersson M, Berinder K, Bensing S, Hoybye C, Eden-Engstrom B, Burman P, Bonelli L, Follin C, Petranek D, Erfurth EM, Wahlberg J, Ekman B, Akerman AK, Schwarz E, Bryngelson IL, Johannsson G (2019) Overall and disease-specific mortality in patients with cushing disease: a swedish nationwide study. J Clin Endocrinol Metab 104(6):2375–2384
3. Nieman LK, Biller BM, Findling JW, Murad MH, Newell-Price J, Savage MO, Tabarin A, Endocrine S (2015) Treatment of
cushing’s syndrome: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 100(8):2807–2831

4. Ritzel K, Beuschlein F, Mickisch A, Osswald A, Schneider HJ, Schopohl J, Reinecke M (2013) Clinical review: outcome of bilateral adrenalectomy in Cushing’s syndrome: a systematic review. J Clin Endocrinol Metab 98(10):3939–3948

5. Reinecke M, Ritzel K, Osswald A, Berr C, Stallgra G, Hallfeldt K, Reisch N, Schopohl J, Beuschlein F (2015) A critical reappraisal of bilateral adrenalectomy for ACTH-dependent Cushing’s syndrome. Eur J Endocrinol 173(4):M23–32

6. Nelson DH, Meakin JW, Dealy JB Jr, Matson DD, Emerson K Jr, Thorn GW (1958) ACTH-producing tumor of the pituitary gland. N Engl J Med 259(4):161–164

7. Guerin C, Taieb D, Treglia G, Brue T, Lacroix A, Sebag F, Castinetti F (2016) Bilateral adrenalectomy in the 21st century: when to use it for hypercortisolism? Endocr Relat Cancer 23(2):R131–142

8. Katznelson L (2015) Bilateral adrenalectomy for Cushing’s disease. Pituitary 18(2):269–273

9. Banaiai MJ, Malek AR (2007) Nelson syndrome: comprehensive review of pathophysiology, diagnosis, and management. Neurosurg Focus 23(3):E13

10. Assie G, Bahurel H, Bertherat J, Kujas M, Legmann P, Bertagna X (2013) Effect of stereotactic radiotherapy and prophylactic pituitary irradiation in adrenocorticotropin-dependent Cushing’s syndrome. J Clin Endocrinol Metab 98(10):3939–3948

11. Assie G, Bahurel H, Bertherat J, Kujas M, Legmann P, Bertagna X (2013) Effect of stereotactic radiotherapy and prophylactic pituitary irradiation in adrenocorticotropin-dependent Cushing’s syndrome. J Clin Endocrinol Metab 98(10):3939–3948

12. Ritzel K, Beuschlein F, Mickisch A, Osswald A, Schneider HJ, Schopohl J, Hallfeldt K, Reinecke M, Ritzel K, Osswald A, Berr C, Stallgra G, Hallfeldt K, Reisch N, Schopohl J, Beuschlein F (2015) A critical reappraisal of bilateral adrenalectomy for ACTH-dependent Cushing’s syndrome. Eur J Endocrinol 173(4):M23–32

13. Nelson DH, Meakin JW, Dealy JB Jr, Matson DD, Emerson K Jr, Thorn GW (1958) ACTH-producing tumor of the pituitary gland. N Engl J Med 259(4):161–164

14. Kemink L, Pieters G, Hermus A, Smals A, Kloppenborg P (1994) Meta-analysis of patients treated for Cushing’s disease. Arch Intern Med 154(16):1982–1987

15. Balduzzi S, Rucker G, Schwarzer G (2019) How to perform a meta-analysis: a practical tutorial. Evid Based Ment Health 22(4):153–160

16. Lau J, Ioannidis JP, Schmid CH (1998) Summing up evidence: one answer is not always enough. Lancet 351(9096):123–127

17. Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315(7109):629–634

18. Wells GA SB, O’Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

19. Balsevski Z, Rucker G, Schwarzer G (2019) How to perform a meta-analysis with R: a practical tutorial. Evid Based Ment Health 22(4):153–160

20. Kemink L, Pieters G, Hermus A, Smals A, Kloppenborg P (1994) Meta-analysis with R: a practical tutorial. Evid Based Ment Health 22(4):153–160

21. Kemink L, Pieters G, Hermus A, Smals A, Kloppenborg P (1994) Meta-analysis with R: a practical tutorial. Evid Based Ment Health 22(4):153–160

22. Kemink L, Pieters G, Hermus A, Smals A, Kloppenborg P (1994) Meta-analysis with R: a practical tutorial. Evid Based Ment Health 22(4):153–160

23. Kemink L, Pieters G, Hermus A, Smals A, Kloppenborg P (1994) Meta-analysis with R: a practical tutorial. Evid Based Ment Health 22(4):153–160

24. Kemink L, Pieters G, Hermus A, Smals A, Kloppenborg P (1994) Meta-analysis with R: a practical tutorial. Evid Based Ment Health 22(4):153–160

25. Jordan RM, Cook DM, Kendall JW, Kerber CW (1979) Nelson’s syndrome and spontaneous pituitary tumor infarction. Arch Intern Med 139(3):340–342

26. Barnett AH, Livesey JH, Friday K, Donald RA, Espiner EA (1983) Comparison of preoperative and postoperative ACTH concentrations after bilateral adrenalectomy in Cushing’s disease. Clin Endocrinol (Oxf) 18(3):301–305

27. Kasperlik-Zaluska AA, Niełubowicz J, Wsiafwskij H, Hartwig W, Zaluska J, Jeske W, Migalska B (1983) Nelson’s syndrome: incidence and prognosis. Clin Endocrinol (Oxf) 19(6):693–698

28. Fountas A, Karavitaki N (2020) Nelson’s syndrome: an update. Endocr Pract 26(4):R131–142

29. Kuhn JM, Proeschel MF, Seurin DJ, Bertagna XY, Luton JP, Girard FL (1989) Comparative assessment of ACTH and lipotropin plasma levels in the diagnosis and follow-up of patients with Cushing’s syndrome: a study of 210 cases. Am J Med 86(6 Pt 1):678–684

30. Grabner P, Hauersjensen M, Jervell J, Flatmark A (1991) Long-term results of treatment of cuscings-disease by adrenalectomy. Acta Chirurgicae- Eur J Surgery 157(8):461–464

31. McCance DR, Russell CF, Kennedy TL, Hadden DR, Kennedy L, Atkinson AB (1993) Bilateral adrenalectomy: low mortality and morbidity in Cushing’s disease. Clin Endocrinol 39(3):315–321

32. Zeiger MA, Fraker DL, Pass HI, Nieman LK, Cutler GB Jr, Chrousos GP, Norton JA (1993) Effective reversibility of the signs and symptoms of hypercortisolism by bilateral adrenalectomy. Surgery 114(6):1138–1143

33. Favia G, Boscaro M, Lumachi F, D’Amico DF (1994) Role of bilateral adrenalectomy in Cushing’s disease. World J Surg 18(4):462–466

34. Kemink L, Pieters G, Hermus A, Smals A, Kloppenborg P (1994) Patient’s age is a simple predictive factor for the development of Nelson’s syndrome after total adrenalectomy for Cushing’s disease. J Clin Endocrinol Metab 79(3):887–889

35. Misra D, Kapur MM, Gupta DK (1994) Incidence of Nelson’s syndrome and residual adrenocortical function in patients of Cushing’s disease after bilateral adrenalectomy. J Assoc Physicians India 42(4):304–305

36. Jenkins PJ, Trainer PJ, Plowman PN, Shand WS, Grossman AB, Wass JA, Besser GM (1995) The long-term outcome after adrenalectomy and prophylactic pituitary radiotherapy in adrenocorticotropin-dependent Cushing’s syndrome. J Clin Endocrinol Metab 80(1):165–171

37. Pereira MA, Halpern A, Salgado LR, Mendonca BB, Nery M, Liberman B, Streelen DH, Wajchenberg BL (1998) A study of patients with Nelson’s syndrome. Clin Endocrinol (Oxf) 49(4):533–539

38. Imai T, Kikumori T, Funahashi H, Nakao A (2000) Surgical management of Cushing’s syndrome. Biomed Pharmacother 54(1):140–145

39. Nageswar SK, van Seters AP, Kievit J, Hermans J, Krans HM, van de Velde CJ (2000) Long-term results of total adrenalectomy for Cushing’s disease. World J Surg 24(1):108–113

40. Hofmann BM, Fahrbusch R (2006) Treatment of Cushing’s disease: A retrospective clinical study of the latest 100 cases. Pituitary Surgery - A Modern Approach 34:158–184

41. Thompson SK, Hayman AV, Ludlam WH, Deveney CW, Loriaux DL, Sheppard BC (2007) Improved quality of life after bilateral laparoscopic adrenalectomy for Cushing’s disease: a 10-year experience. Ann Surg 245(5):790–794

42. Ding XF, Li HZ, Yan WG, Gao Y, Li XQ (2010) Role of adrenalectomy in recurrent Cushing’s disease. Chin Med J 123(13):1658–1662

43. Osswald A, Plomer E, Dimopoulou C, Milius M, Blaser R, Ritzel K, Mickisch A, Knerr F, Stanojevic M, Hallfeldt K, Schopohl J,
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Kuhn KA, Stall G, Beuschlein F, Reincke M (2014) Favorable long-term outcomes of bilateral adrenalectomy in Cushing’s disease. Eur J Endocrinol 171(2):209–215
44. Prajapati OP, Verma AK, Mishra A, Agarwal G, Agarwal A, Mishra SK (2015) Bilateral adrenalectomy for Cushing’s syndrome: pros and cons. Indian J Endocrinol Metabol 19(6):834–840
45. Espinosa-de-Los-Monteros AL, Sosa-Erozoa E, Espinosa E, Mendoza V, Arreola R, Mercado M (2017) Long-term outcome of the different treatment alternatives for recurrent and persistent cushing disease. Endocrine Pract: Off J Am College Endocrinol Am Assoc Clin Endocrinol 23(7):759–767
46. Grafteo CS, Perry A, Carlstrom LP, Meyer FB, Atkinson JLD, Erickson D, Nippoldt TB, Young WF, Pollock BE, Van Gompel JI (2017) Characterizing and predicting the Nelson-Salassa syndrome. J Neurosurg 127(6):1277–1287
47. Nankova A, Yaneva M, Elenkova A, Marinov M, Hadzhianeve A, Sechanov T, Gantchev G, Todorov G, Kirilov G, Kalinov K, Andreeva M, Zacharieva S (2018) Cushing’s syndrome: a historic review of the treatment strategies and corresponding outcomes in a single tertiary center over the past half-century. Hormone Metab Res 50(4):280–289
48. Chiloiro S, Giampietro A, Tcharaktchiev D, Marinov M, Hadzhianeve A, Sechanov T, Gantchev G, Todorov G, Kirilov G, Kalinov K, Andreeva M, Zacharieva S (2018) Cushing’s syndrome: a historic review of the treatment strategies and corresponding outcomes in a single tertiary center over the past half-century. Hormone Metab Res 50(4):280–289
49. Cohen AC, Goldney DC, Danilowicz K, Manavela M, Rossi MA, Chiloiro S, Giampietro A, Raffaelli M, D’Amato G, Bima C, Nankova A, Yaneva M, Elenkova A, Tcharaktchiev D, Marinov M, Hadzhianeve A, Sechanov T, Gantchev G, Todorov G, Kirilov G, Kalinov K, Andreeva M, Zacharieva S (2018) Cushing’s syndrome: a historic review of the treatment strategies and corresponding outcomes in a single tertiary center over the past half-century. Hormone Metab Res 50(4):280–289
50. Nagendra L, Bhavani N, Pavithran PV, Kumar GP, Menon UV, Nelson’s syndrome. Arch Endocrinol Metab 63(5):470–477
51. Kuhn KA, Stall G, Beuschlein F, Reincke M (2014) Favorable long-term outcomes of bilateral adrenalectomy in Cushing’s disease: a reappraisal of Nelson’s Syndrome. J Clin Endocrinol Metab 92(1):172–179
52. Assie G, Bahurel H, Coste J, Silvera S, Kujas M, Dugue MA, Sarkis P, Rabilloud M, Lifante JC, Siamand A, Jouanneau E, Gay CK, Mavuduru R, Kumar S, Behera A, Saikia UN, Dhandapani S, Wali R (2020) ACTH increment post total bilateral adrenalectomy for Cushing’s disease: a consistent biosignature for predicting Nelson’s syndrome. Pituitary 23(5):488–497
53. Barber TM, Adams E, Ansorge O, Byrne J, Karavitaki N, Wass JA (2010) Nelson’s syndrome. Eur J Endocrinol 163(4):495–507
54. Reincke M, Albanì A, Assie G, Bancos I, Brue T, Buchfelder M, Chabre O, Ceccato F, Daniele A, Detomas M, Di Dalmazi G, Elenkova A, Follin E, Grossman AB, Gomez-Sanchez CE, Heaney AP, Honegger J, Karavitaki N, Lacroix A, Laws ER, Lacroix A, Laws ER, Losa M, Murakami M, Newell-Price J, Pecori Giraldi F, Perez-Rivas LG, Pivonello R, Rainey WE, Sbiera S, Schopohl J, Stratakis CA, Theodoropoulou M, van Rossum EFC, Valassi E, Zacharieva S, Rubinstein G, Ritzel K (2021) Corticotroph tumor progression after bilateral adrenalectomy (Nelson’s syndrome): systematic review and expert consensus recommendations. Eur J Endocrinol. https://doi.org/10.1530/EJE-20-1088
55. Patel J, Eloy JA, Liu JK (2015) Nelson’s syndrome: a review of the clinical manifestations, pathophysiology, and treatment strategies. Neurosurg Focus 38(2):E14
56. Fountas A, Lim ES, Drake WM, Powlson AS, Gurnell M, Martin NM, Seejoe K, Murray RD, MacFarlane J, Alhumaidi S, Swords F, Ashraf M, Pal A, Cong Z, Freed M, Balafshani T, Purewal TS, Speak RG, Newell-Price J, Higham CE, Hussein Z, Baldeweg SE, Dales J, Reddy N, Levy MJ, Karavitaki N (2020) Outcomes of patients with Nelson’s syndrome after primary treatment: a multicenter study from 13 UK pituitary centers. J Clin Endocrinol Metab 105(5):1527–1537

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