Usefulness of desmopressin testing to predict relapse during long-term follow-up in patients in remission from Cushing’s disease

Alberto Giacinto Ambrogio¹, Massimiliano Andrioli¹, Martina De Martin¹, Francesco Cavagnini¹ and Francesca Pecori Giraldi¹²

¹Neuroendocrinology Research Laboratory, Istituto Auxologico Italiano IRCCS, Milan, Italy
²Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy

Abstract

Recurrence of Cushing’s disease after successful transsphenoidal surgery occurs in some 30% of the patients and the response to desmopressin shortly after surgery has been proposed as a marker for disease recurrence. The aim of the present study was to evaluate the response to desmopressin over time after surgery. We tested 56 patients with Cushing’s disease in remission after transsphenoidal surgery with desmopressin for up to 20 years after surgery. The ACTH and cortisol response to desmopressin over time was evaluated in patients on long-term remission or undergoing relapse; an increase by at least 27 pg/mL in ACTH levels identified responders. The vast majority of patients who underwent successful adenomectomy failed to respond to desmopressin after surgery and this response pattern was maintained over time in patients on long-term remission. Conversely, a response to desmopressin reappeared in patients who subsequently developed a recurrence of Cushing’s disease, even years prior to frank hypercortisolism. It appears therefore that a change in the response pattern to desmopressin proves predictive of recurrence of Cushing’s disease and may indicate which patients require close monitoring.

Introduction

First-line treatment of Cushing’s disease is surgical removal of the ACTH-secreting pituitary tumor and worldwide remission rates range from 60 to 80% (1, 2, 3). The tumor may recur, however, most often within two years of surgery but sometimes even decades after cure. Estimates of recurrence vary from 5 to 30% (4, 5, 6) indicating that up to one-fifth of the patients may experience a relapse of hypercortisolism. From a clinical viewpoint, this translates into the need for long-term surveillance of patients in remission and repeated testing with a variety of hormonal challenges. Indeed, as with the diagnosis of Cushing’s disease, the establishment of recurrence may be straightforward in some patients and challenging in others. This has given rise to the search for reliable markers of recurrence (1, 7), usually at immediate postsurgical testing, but none has proven fully predictive for long-term, relapse-free survival.

One potential recurrence prognostic is desmopressin testing, a procedure also used during the diagnostic work-up of Cushing’s disease. Administration of desmopressin, a long-acting vasopressin analog, has in fact proven useful to distinguish Cushing’s disease from pseudo-Cushing states (8, 9, 10, 11, 12, 13, 14) as it has been shown to stimulate ACTH secretion in tumoral

Correspondence should be addressed to F Pecori Giraldi
Email francesca.pecorigiraldi@unimi.it or fpg@auxologico.it

Key Words
- desmopressin
- Cushing’s disease
- transsphenoidal surgery
- recurrence
corticotropes (15, 16, 17, 18, 19). Along the same line, a response to desmopressin after surgery may be taken to indicate the persistence of tumoral corticotropes (20, 21, 22, 23, 24). Postsurgical desmopressin testing has been used both to establish remission (20, 21, 24) and to predict relapse (22, 23) with testing performed shortly after surgery.

The aim of the present study was to assess the pattern of ACTH/cortisol responses to desmopressin in the years following transsphenoidal surgery in patients with Cushing's disease on long-term remission and to establish whether changes in the response to desmopressin in patients during follow-up can prove an early marker for recurrence.

**Subjects and methods**

**Patients**

We evaluated 56 patients with Cushing's disease (43 women, 13 men, mean age 39.4 ± 1.47 years, range 15–67 years) in remission after transsphenoidal surgery and followed for 2–23 years (mean 130.1 ± 8.93 months). The diagnosis of Cushing's disease had been established by standard diagnostic criteria (4, 25) and confirmed by surgical cure and/or pathology. Outcome of surgery had been established on both clinical and laboratory grounds with testing performed within 5 days of surgery. Patients in remission presented normal urinary-free cortisol (UFC) levels and low-normal morning serum cortisol, signs and symptoms of adrenal insufficiency and required steroid replacement therapy. Replacement therapy was started with cortisone acetate 37.5 mg/daily and mean length of replacement therapy was 14.7 ± 1.78 months after exclusion of 2 patients who could not be weaned off steroid replacement and are currently still being treated at 16 and 17 years after surgery. Patients who subsequently developed elevated UFC, abnormal overnight suppression test (OST; cortisol >3 µg/dL after 1 mg dexamethasone administered at midnight (26)) and clinical signs of hypercortisolism were considered relapse. The first available abnormal UFC was taken to indicate time-to-relapse; relapse occurred 87.0 ± 13.58 months (range 24–162 months) after surgery.

Patients were classified into two groups according to the criteria described above: long-term remission (43 patients) and relapse (13 patients; Table 1); 43 patients (33 remission, 10 relapse) had been tested with desmopressin also prior to surgery. Postsurgical evaluation was performed, usually at yearly intervals, by means of clinical evaluation, UFC measurement, OST and desmopressin testing.

Approval for the present study was obtained by the Ethical Committee of the Istituto Auxologico Italiano and informed consent was obtained from all participants prior to testing.

Desmopressin testing was performed in the morning according to our usual protocol (8, 12). Briefly, 10 µg desmopressin (Ferring Pharmaceuticals) was administered as an i.v. bolus and blood samples for ACTH and cortisol estimation obtained before and 10, 20, 30, 45, 60, 90 and 120 min after drug administration. Blood pressure and heart rate were monitored throughout the procedure. Patients were considered responsive if ACTH increased by at least 27 pg/mL (6 pmol/L) (8). This cut-off yielded the highest diagnostic accuracy to discern patients with Cushing's disease from normal-weight and obese subjects as well as from those with pseudo-Cushing. Given that desmopressin testing in the current setting is used to distinguish recurrence of the corticotrope adenoma vs normal HPA physiology, it appears appropriate to use the same criterion.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic data and early postsurgical evaluation in patients with Cushing's disease.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>Age (years)</td>
</tr>
<tr>
<td>All patients (n=56)</td>
<td>39.4 ± 1.47</td>
</tr>
<tr>
<td>Long-term remission (n=43)</td>
<td>39.1 ± 1.59</td>
</tr>
<tr>
<td>Relapse (n=13)</td>
<td>40.6 ± 3.63</td>
</tr>
</tbody>
</table>

*P<0.05 vs relapse. To convert into SI, multiply urinary-free cortisol by 2.759, serum cortisol by 27.59.
Assays

Plasma ACTH was measured by two-site immunoradiometric assay (Allegro, Nichols Institute Diagnostics, San Juan Capistrano, CA, USA) up to 2010 and then by chemiluminescent immunoassay (Elecys, Roche). Plasma cortisol and UFC, the latter after urine extraction with dichloromethane, were measured by RIA (Byk-Sangtec Diagnostica, Dietzenbach, Germany and DPC, Los Angeles, CA, USA, respectively) until 2010 and then by chemiluminescent immunoassay (Elecys, Roche). Stringent quality control procedures within the laboratory ensured optimal commutability and linearity between assays. Overall, intra- and interassay coefficients of variations are 3.2 and 8.2% for ACTH, 3.0 and 4.7% for serum cortisol and 3.5 and 6.2% for UFC. Normal ranges in our laboratory are 10–50 pg/mL and 9–64 pg/mL for ACTH with immunometric and chemiluminescent assays, respectively, and 10–80 μg/24 h and 17–136 μg/24 h for UFC with immunometric and chemiluminescent assays, respectively; normal range for serum cortisol is 5–25 μg/dL with either assay.

Statistical analyses

The ACTH and cortisol responses to DDAVP were evaluated as absolute peak, absolute increment and percentage increment compared to basal values. Student’s t-test for paired data was used for comparisons of ACTH concentrations in the same patient, whereas non-parametric tests, i.e., Mann-Whitney and Wilcoxon, were used, as appropriate, for the analysis of derived variables. Chi-square and Fisher’s exact tests were used for comparison of qualitative variables. Logistic regression analysis was performed to identify predictor variables; Receiver Operator Characteristic (ROC) analysis was performed to establish diagnostic efficiency and calculate Youden’s J index (27). Data are expressed as mean ± s.e. or median and 25th/75th centile range. Statistical significance was accepted for P < 0.05. Statistical analyses were performed with Statview (SAS Institute, Cary NC, USA) and MedCalc (MedCalc Software, Ostend, Belgium).

Results

Early postoperative evaluation

Table 1 shows hormonal data in patients upon early postsurgical evaluation. i.e., <1 week after surgery. As expected, UFC, and morning and midnight serum cortisol as well as cortisol after OST were significantly lower compared to presurgical levels in all patients (UFC 20.3 ± 1.74 vs 416.1 ± 58.18 μg/24 h, respectively, P < 0.0001; morning cortisol 4.73 ± 0.641 vs 19.9 ± 1.12 μg/dL, P < 0.0001; midnight cortisol 1.76 ± 0.234 vs 18.6 ± 1.38 μg/dL, P < 0.0001; cortisol after OST 1.22 ± 0.116 vs 16.4 ± 1.69 μg/dL, P < 0.0001). No significant differences in immediate postoperative UFC or morning serum cortisol values were observed between patients on long-term remission or relapse; conversely, midnight serum cortisol and cortisol after OST levels were higher in patients who relapsed (Table 1). No differences in length of replacement therapy were observed between patients in long-term remission and relapse (17.2 ± 2.18 vs 13.6 ± 3.06 months, N.S., after exclusion of 2 patients still on replacement therapy, as described earlier).

Forty-seven patients underwent the desmopressin test immediately after surgery and the ACTH peak increment decreased on average from 176.8 ± 32.49 pg/mL before surgery to 14.7 ± 3.61 pg/mL after surgery (P < 0.001). Comparison of pre- and postsurgical responses revealed that the response to desmopressin disappeared in all but 6 patients, 4 long-term remissions (last follow-up 44–94 months) and 2 relapses (Fig. 1). Overall, the ACTH response to desmopressin was comparable between patients on long-term remission and relapses (incremental peak 14.6 ± 4.27 vs 9.4 ± 2.08 pg/mL, N.S., respectively) as was the percentage of non-responders (88.9 vs 80%, P = 0.61 by Fisher’s exact test). Analysis of the ACTH response as percentage over baseline also did not differ (209.6 ± 20.51 vs 197.9 ± 29.68%, N.S., for remission and relapse, respectively), nor did the cortisol response (incremental peak 2.32 ± 0.66 vs 2.66 ± 0.85 μg/dL, percent increase 148.7 ± 16.62 vs 175.7 ± 29.66%, N.S., for remission and relapse, respectively). In fact, no variable was retained at the stepwise entry logistic regression analysis except for OST (coefficient −1.253 ± 0.618, P < 0.05). It follows that the response to desmopressin observed at early postoperative evaluation was not predictive of long-term remission in our series.

Long-term evaluation

All patients underwent desmopressin testing during postsurgical follow-up for up to 275 months; in total, 309 tests were performed. Patients in long-term remission displayed comparable responses over time (Fig. 2, left panel) and, indeed, no discernible differences in ACTH peak increment were observed at repeated-measures ANOVA.
(F = 1.46, N.S., Fig. 2, right panel). Of note, in patients in long-term remission, no differences were observed between tests performed prior to 2010 (immunoradiometric assay, \( n = 194 \)) and after 2010 (chemiluminescent immunoassay; \( n = 44 \)) as regards baseline ACTH concentrations (25.7 ± 1.81 vs 23.63 ± 1.79 pg/mL, N.S.), ACTH peak (65.8 ± 8.44 vs 47.6 ± 5.37 pg/mL, N.S.) and ACTH peak increment (40.1 ± 7.51 vs 23.97 ± 4.28 pg/mL, N.S.). Likewise, no differences were observed for cortisol concentrations measured before (radioimmunoassay) and after 2010 (chemiluminescent immunoassay) at baseline (8.8 ± 0.52 vs 8.7 ± 0.36 µg/dL, N.S.), peak (14.1 ± 0.94 vs 13.2 ± 0.87 µg/dL, N.S.) and incremental peak (5.3 ± 0.55 vs 4.5 ± 0.69 µg/dL, N.S.).

As regards individual responses, in addition to the 4 patients tested early after surgery who displayed persistent ACTH responses to desmopressin although in remission, 5 additional patients in long-term remission (follow-up 75–273 months) presented responses to desmopressin at postsurgical evaluations; this pattern did not change over
the entire observation period. In all other patients, even 10 years after surgery, the ACTH response to desmopressin fell easily within the range of responses recorded in normal subjects (median incremental peak 14.9 pg/mL, 10th centile: 4.8 pg/mL, 90th centile: 27.0 pg/mL (8)). Patients who did not respond to desmopressin prior to surgery maintained this response pattern throughout (follow-up range 2–7 years).

Conversely, the response pattern to desmopressin changed over time in patients who relapsed (time-to-relapse 24–162 months). At early postsurgical evaluation, patients had failed to mount a significant response to desmopressin and had thus been considered non-responders (as described earlier, Fig. 3). However, the response pattern changed over time and clear-cut ACTH increases were registered at different time points after surgery (Fig. 3). Once the response pattern had changed to responder status, this trend was confirmed at subsequent testing; indeed, all patients were responsive to desmopressin by the time of relapse (average incremental peak 97.1 ± 27.46 pg/mL; Fig. 3). Most interestingly, in 9 patients with multiple testing, the response to desmopressin had become evident prior to the recurrence of hypercortisolism (Fig. 3). In fact, UFC and OST were indicative of normal HPA axis function at the time the response to desmopressin changed and became clearly altered only months to years after this first response (Table 2).

As mentioned earlier, the criterion for response to desmopressin was chosen on the basis of the response observed in normal subjects (8) and, indeed, patients in remission retained a pattern consistent with normal HPA secretion (as described earlier). We also performed the ROC analysis on our chosen criterion, in comparison with the percent ACTH increase, as used by other investigators (20). Comparison of ROC curves revealed that absolute ACTH increase was superior to percent ACTH increase (ROC AUC 0.836 ± 0.0341 vs 0.713 ± 0.0434, \( P < 0.001 \), respectively, Supplementary Fig. 1, see section on supplementary data given at the end of this article). Indeed, Youden’s index for absolute ACTH increase was indicative of good diagnostic effectiveness at 0.685 (95% C.I. 0.563; 0.776), whereas the same parameter for percent ACTH increase was far lower 0.3926 (95% C.I. 0.243; 0.506).

### Table 2 Hormonal responses in patients who experienced recurrence in whom the response to desmopressin preceded full-blown hypercortisolism.

<table>
<thead>
<tr>
<th>Pt #</th>
<th>Reappearance of response to desmopressin* Months after surgery</th>
<th>ACTH incremental peak ACTH in (pg/mL)</th>
<th>UFC (µg/24h)</th>
<th>OST (µg/dL)</th>
<th>Relapse Months after surgery</th>
<th>ACTH incremental peak ACTH in (pg/mL)</th>
<th>UFC (µg/24h)</th>
<th>OST (µg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>102</td>
<td>57.3</td>
<td>41.0</td>
<td>0.9</td>
<td>147</td>
<td>73</td>
<td>147</td>
<td>4.6</td>
</tr>
<tr>
<td>2</td>
<td>16</td>
<td>30.9</td>
<td>35.5</td>
<td>1.2</td>
<td>29</td>
<td>103.6</td>
<td>188</td>
<td>3.5</td>
</tr>
<tr>
<td>3</td>
<td>80</td>
<td>46.1</td>
<td>50.7</td>
<td>2</td>
<td>108</td>
<td>48.4</td>
<td>134</td>
<td>5.9</td>
</tr>
<tr>
<td>4</td>
<td>66</td>
<td>43.1</td>
<td>28.8</td>
<td>0.9</td>
<td>162</td>
<td>397</td>
<td>1035</td>
<td>9.6</td>
</tr>
<tr>
<td>5</td>
<td>34</td>
<td>31.9</td>
<td>23.8</td>
<td>0.7</td>
<td>115</td>
<td>173</td>
<td>693</td>
<td>8.4</td>
</tr>
<tr>
<td>6</td>
<td>18</td>
<td>29</td>
<td>46</td>
<td>2.7</td>
<td>44</td>
<td>47.1</td>
<td>267</td>
<td>11.1</td>
</tr>
<tr>
<td>7</td>
<td>59</td>
<td>27.7</td>
<td>60.4</td>
<td>2</td>
<td>85</td>
<td>30.3</td>
<td>180</td>
<td>7.8</td>
</tr>
<tr>
<td>8</td>
<td>80</td>
<td>28.4</td>
<td>31.6</td>
<td>0.9</td>
<td>116</td>
<td>84.4</td>
<td>430</td>
<td>3.5</td>
</tr>
<tr>
<td>9</td>
<td>25</td>
<td>31.5</td>
<td>13.3</td>
<td>1.0</td>
<td>36</td>
<td>46.1</td>
<td>460</td>
<td>11.7</td>
</tr>
</tbody>
</table>

*Criteria for response: ACTH peak increment >27 pg/mL. UFC: urinary-free cortisol (abnormal > 80 µg/24h); OST: cortisol after 1 mg dexamethasone (abnormal > 3 µg/dL (26)).

To convert into SI, multiply urinary-free cortisol by 2.759, serum cortisol by 27.59.
Discussion

The management of patients with Cushing’s disease requires considerable expertise. First, diagnosis of endogenous cortisol excess is by no means straightforward (25), especially in mild cases (28), and then transsphenoidal surgery – the first choice treatment – has to prove successful. Furthermore, once the patient is in remission, the specter of relapse has to be taken into account and patients monitored for years (29). In this context, while relapse may sometimes occur rapidly, in most cases this appears a rather slow, lengthy process and repeated evaluations have to be performed over time until full-blown hypercortisolism is unmistakably manifest. The physician may therefore have to assess pituitary–adrenal function for years, which is costly and possibly unnecessary if patients do not relapse. Several criteria have been proposed to establish which patients are at risk for relapse and warrant close follow-up and which are unlikely to present disease recurrence and can be monitored more loosely. Morning serum cortisol after surgery (30) is one such criterion, although prediction is by no means absolute (31) as up to 25% of the patients with undetectable/low cortisol relapse at a future date (5, 32). Other criteria have also been proposed as predictors of relapse, such as findings at pathology (2), response to CRH (4, 33), inhibition after 1 mg dexamethasone overnight (34, 35), plasma ACTH levels (36) and late-night salivary cortisol (37). None however provides absolute certainty for relapse-free survival and the search for more accurate indicators is on-going.

One recent addition to the panel of predictors is the postsurgical response to desmopressin. This test has proven useful to distinguish patients with Cushing’s disease from patients with pseudo-Cushing (11, 28) and there are also several studies reporting its use after surgery. Stimulation with desmopressin shortly after surgery may help confirm successful removal of tumoral corticotropes, as the response to desmopressin is expected to disappear in these patients (20, 21, 23). Conversely, if the response to desmopressin persists after surgery, then failure is likely (20, 21, 23). Overall, some 50–80% of individuals who presented a response to desmopressin though in remission subsequently relapsed (20, 23); thus, the test appeared a possible but not fully reliable predictor. Moreover, no specific cut-off could be identified; indeed, criteria for response varied from absolute cortisol increase over 7 µg/dL (23) to percentage ACTH and cortisol increase over 30% and 20%, respectively (20). Variants of desmopressin stimulation, i.e., dexamethasone-suppressed desmopressin stimulation, have also been proposed but again results proved promising though not fully predictive of surgical outcomes (38, 39).

It appears, therefore, that immediate postsurgical evaluation may not be the best timeframe to predict an occurrence which may take place years after surgery. In fact, it has been suggested that subtle alterations of the hypothalamic–pituitary–adrenal axis may develop over time and represent an early predictor of relapse (40), thus identifying patients who necessitate closer monitoring. We decided to review the response pattern to desmopressin in a large series of patients with Cushing’s disease in remission after pituitary surgery in order to identify whether the response to desmopressin may represent an early marker of relapse and, indeed, can state that this is the case.

On the one hand, analysis of response patterns in patients in stable, long-term remission showed that the response to desmopressin is modest and that this response pattern is maintained for years, even decades. The small increase in ACTH upon desmopressin stimulation, indeed, is reminiscent of the response observed in normal subjects (8), supporting the concept that normal hypothalamic–pituitary–adrenal axis physiology is restored in patients on long-term remission (41).

Conversely, patients who relapsed changed their response pattern over time. In fact, although ACTH failed to increase at immediate postsurgical evaluation in these patients – in keeping with remission status – ACTH peak levels increased at subsequent testing. This represented a clear deviation from the previous, bland response pattern, suggesting a reprise of the ACTH secretory response typical to Cushing’s disease. Indeed, as both normal individuals and patients in remission from Cushing’s disease do not mount a significant ACTH secretory response after desmopressin stimulation, a deviation from this pattern is highly informative.

Several mechanisms have been postulated to underlie this peculiar secretory response. Desmopressin has a strong affinity for the vasopressin V2 and V3 receptor subtypes (42, 43) and available evidence points to an involvement of both receptors in the stimulatory effect of desmopressin on ACTH secretion by tumoral corticotropes (16, 17, 44). On the other hand, mechanisms other than direct desmopressin action at the pituitary level have been postulated given that some patients fail to respond to desmopressin in vitro notwithstanding a clear in vivo response (16). In these patients, relapse would imply
re-enacting the deregulation in suprapituitary control mechanisms which enables the response to desmopressin, reminiscent of the hypothalmo-derived hypothesis for corticotrope tumor pathogenesis (45, 46).

In the present study, we applied the criterion developed to diagnose patients with Cushing’s disease prior to surgery (8) to identify a response to desmopressin after surgery. This strategy is in line with other studies (20, 38) and proved rational as patients in long-term remission presented a modest – if any – increase in ACTH upon desmopressin stimulation, well within the range observed in normal subjects. Indeed, ROC curve analysis and Youden’s index confirmed its good diagnostic effectiveness and superiority to percent ACTH increase.

Of note, reappearance of the ACTH response to desmopressin occurred months to years prior to full-blown recurrence of hypercortisolism; indeed, the interval between the appearance of a response to desmopressin and detection of increased UFC levels or absent OST suppression ranged from 1 to 8 years in patients tested at regular intervals. A similar pattern had been observed in 2 patients reported by Dall’Asta (47) and in some patients submitted to dexamethasone-suppressed desmopressin testing (48). Reappearance of the response to vasopressin analogs and/or to CRH prior to overt recurrence had also been reported in some patients from a French series (40). This suggests that corticotrope tumor cell re-growth is associated with deregulation of the response to desmopressin quite some time before giving rise to excess cortisol secretion. It follows that repeat desmopressin testing in patients in remission is useful to identify patients who mandate closer monitoring and those who can be followed more loosely. A shift toward desmopressin responsiveness in patients who previously failed to respond is likely to be followed by recurrence of hypercortisolism and should prompt careful surveillance allowing timely detection of relapse. Conversely, constant, absent responses to desmopressin may allow a less strict monitoring schedule. Interestingly, changes in late-night salivary cortisol have also been reported to herald full-blown recurrence of hypercortisolism although there is considerable variability in salivary cortisol sequential measures (49, 50). One study reported that responses to vasopressin analogs preceded changes in midnight salivary cortisol in 8 out of 14 patients (40); thus, there might indeed be a specific advantage to desmopressin testing as an early predictor of disease recurrence. Definition of threshold markers and timing of testing for desmopressin as well as other predictive parameters will require further large-scale, and possibly collaborative, studies.

In conclusion, our study has shown that patients with Cushing’s disease on long-term surgical remission maintain their response pattern to desmopressin over time. Conversely, a change in the response pattern over time anticipates a recurrence of Cushing’s disease. Reappearance of the response to desmopressin represents an alert for closer monitoring.

Supplementary data
This is linked to the online version of the paper at http://dx.doi.org/10.1530/EC-17-0292.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the reported research. FPG received Advisory Board Member honoraria from Novartis and HRA Pharma.

Funding
This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

References
DDAVP test as a predictor of recurrence


Chen JCT, Amar AP, Choi S, Singer P, Couldwell WT & Weiss MH. Transsphenoidal microsurgical treatment of Cushing disease: postoperative assessment of surgical efficacy by application of an

http://www.endocrineconnections.org

© 2017 The authors
Published by Bioscientifica Ltd

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.


---

**Received in final form 9 October 2017**

**Accepted 10 October 2017**

**Accepted preprint published online 10 October 2017**