Dexamethasone-related adrenal insufficiency in patients with solid brain tumours

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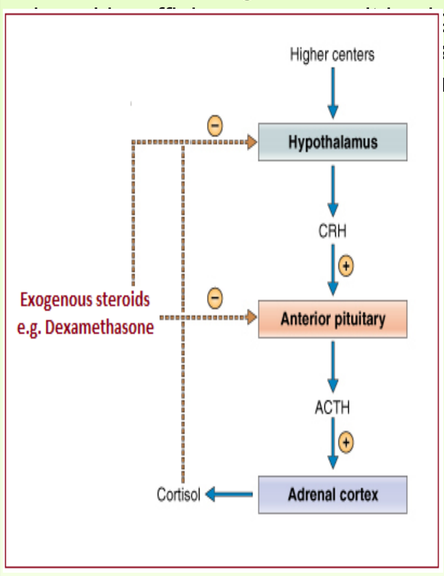
INTRODUCTION

Primary brain tumours, although fairly uncommon (8 per 100,000 per year) comprise the 8th most common cancer of people of working age (16-65) and the fifth most common cause of death from cancer in under 65s. The mainstay of treatment for primary brain tumours is surgical excision and radiotherapy, and in two thirds of patients, steroids (dexamethasone) is used to reduce cerebral oedema and to help relieve the symptoms of raised intracranial pressure such as headache and vomiting. Long term use of high dose exogenous steroids in such a manner can cause suppression of the hypothalamic-pituitary-adrenal (HPA) axis impacting both on corticotrophin-releasing hormone (CRH) and adrenocorticotrophic hormone (ACTH) as demonstrated below.

With prolonged suppression of the HPA axis, adrenal glands eventually atrophy and can take months to years to recover some degree of functioning. Undiagnosed [illegible] significant morbidity [illegible]sis if steroids are [illegible]ment regimen.



Patients with adrenal insufficiency are identified biochemically by a failed short synacthen test (SST). This involves taking a basal level of cortisol, then giving 250ïg synacthen either I.V. or I.M. Samples of cortisol are then taken at 30 minutes. A failed SST is the inability to raise serum cortisol over 550nM/L at 30 minutes.

RATIONALE

Although corticosteroids like dexamethasone are used to treat peritumoral oedema, there are currently no specific guidelines on their use (i.e. dose and duration). The endocrinology department at the University Hospital Birmingham identified a gap in literature regarding the relationship between adrenal insufficiency and long term steroid use in patients being weaned off steroid regimens. They believe that it is necessary to devise a set of departmental guidelines regarding the steroid dose and/or duration that will be necessary to prevent adrenal

AIMS AND OBJECTIVES

1. To determine the median dose, duration and dexamethasone exposure in both groups: those who passed their SST and those who failed.
2. To determine whether there is a significance difference in the baseline cortisol, 30 minute cortisol, median dose, median duration and median total steroid exposure between the 2 groups.
3. To propose a dose and/or duration of steroid exposure that may prevent adrenal insufficiency.

METHODS

BIOCHEMISTRY LISTS All patients with SST between October 2010-2012

INFORMATICS Clinic codes used to determine patients who attended endocrinology brain tumour clinics

PASS/FAIL SST: Patients categorized as pass or fail based on whether their 30 min cortisol was above or below 550nM/L

CLINICAL PORTAL: A retrospective evaluation of patient records. Patients with solid brain tumour were included; those with pituitary tumours were excluded.

Information on demographics, diagnosis, baseline and 30 minute cortisol, steroid type, dose and duration of treatment was obtained for each patient. Every time the dose was altered, this was recorded to give an end result of area under the curve i.e. total steroid exposure. Statistical analysis was then carried out to see if there was any significant difference between the pass and fail groups.

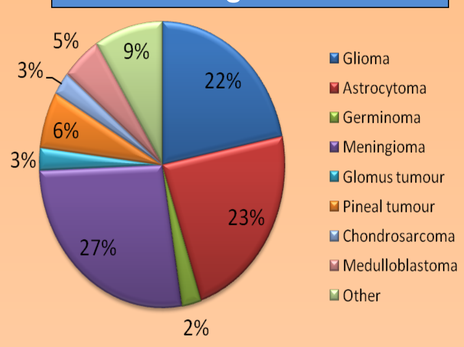
RESULTS

Patient Characteristics

Biochemistry lists identified 1,164 patients who had SSTs between October 2010 and October 2012. Informatics used specific clinic codes to identify patients who had attended brain tumour endocrinology clinics. After review on clinical portal, a total of 78 patients were obtained that fit the selection criteria. Of this study population of 78, 53 patients passed their SST and 25 failed.

	PASSED SST	FAILED SST
NO. OF PATIENTS	53	25
M:F	22:31	12:13

Solid Brain Tumour Diagnosis



The pie chart above shows the confirmed diagnosis of all patients in both the pass and fail groups

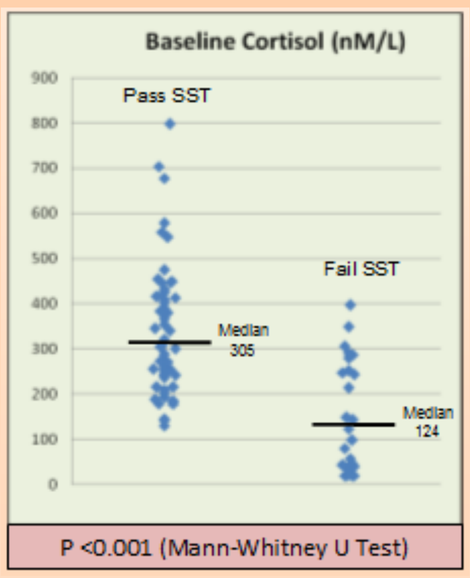
Correlation tests: Spearman and Pearson's

	Spearman's Correlation	Pearson's Correlation
	Passes vs Fails Coeff. (P-value)	
Baseline cortisol vs duration	-.333 (.003)	-.399 (.000)
Baseline cortisol vs mean	-.151 (.186)	-.134 (.234)
Baseline cortisol vs exposure	-.304 (.007)	-.307 (.006)
30 min cortisol vs duration	-.567 (.000)	-.564 (.000)
30min cortisol vs mean	-.369 (.001)	-.342 (.002)
30 min cortisol vs	-.531 (.000)	-.445 (.000)

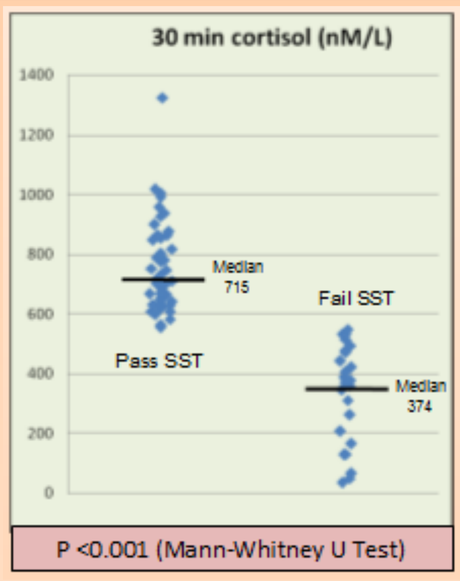
For the criteria shown in the table, when tested in the fail group only, the pass group only and the pass group of those on dexamethasone, there was no significant relationship obtained.

Comparison of those who passed SST and those who failed SST

	PASSED SST	FAILED SST
MEDIAN DEXAMETHASONE DOSE (mg)	0.00 mg (IQR= 2.3mg)	3.30 mg (IQR= 2.70mg)
MEDIAN DURATION OF STEROID TREATMENT (days)	0 days (IQR= 56 days)	360 days (IQR= 390 days)
MEDIAN TOTAL STEROID EXPOSURE (mgdays)	0.00mgdays (IQR= 88 mgdays)	928 mgdays (IQR= 1920 mgdays)



P <0.001 (Mann-Whitney U Test)



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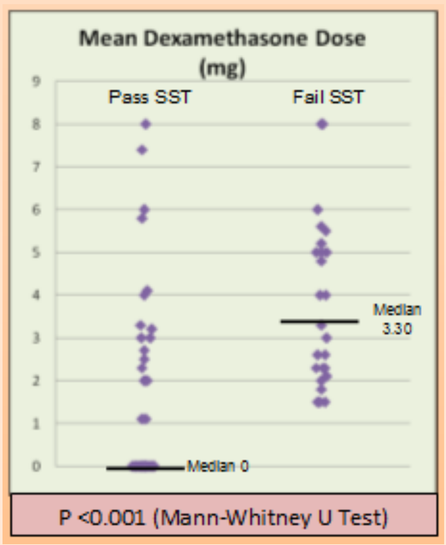

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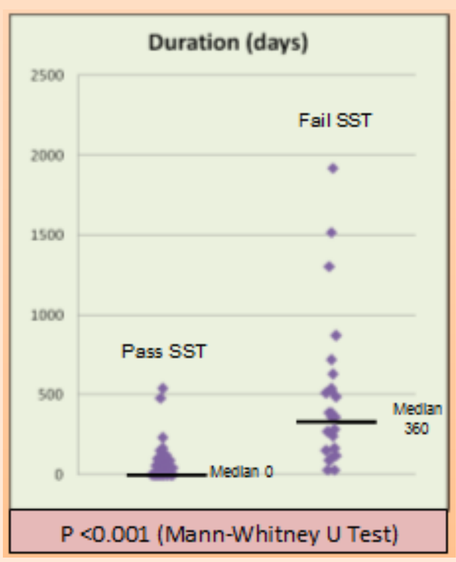

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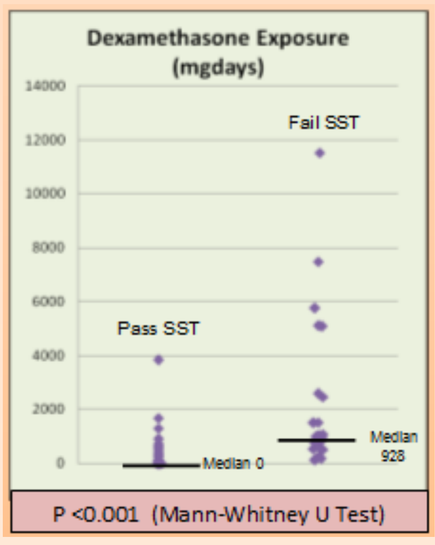

P <0.001 (Mann-Whitney U Test)

SERIAL CHI-SQUARE TESTS

Serial Chi-square tests		
DOSE	2 mg	P = 3.71 x 10^{-5}
DURATION	150 days	P = 2.43 x 10^{-13}
STEROID EXPOSURE	450 mgdays	P= 4.19 x 10^{-9}

DISCUSSION

The primary aim was to determine the relationship between adrenal insufficiency and long term steroid exposure.

The pass and fail groups were compared initially with respect to 5 variables:

- Baseline cortisol
- 30 minute cortisol
- Mean dose
- Mean duration
- Total steroid exposure.

A Mann-Whitney U test compared whether there was a significant difference between the pass and fail groups for the aforementioned variables. Scatterplots show, in all categories, the null hypothesis was rejected; there was a significant difference between those who passed their SST and those who failed.

Spearman's and Pearson's correlation tests were done on all the data to determine whether any correlations existed. Tests were performed first on the pass vs. fail group as a whole. There was a significant negative correlation between baseline cortisol and both steroid duration and exposure. However, no significant correlation existed between baseline cortisol and dose. A significant negative correlation was also noted between 30 minute cortisol and all the variables: duration, dose and exposure. This showed that exposure and duration were more influential factors for failing SST, rather than dose. Spearman and Pearson's correlation tests were then conducted on 2 additional groups: the fail group only and the pass group only. None of the variables showed a significant correlation with baseline cortisol or with 30 minute cortisol.

In the pass group 62% of the subjects (33 out of 53 patients) had a mean dose of 0mg dexamethasone i.e. no exposure. Therefore, Spearman's and Pearson's tests were also carried out on those patients in the pass group who had been exposed to steroids only (the 33 patients who had not were excluded from this correlation). This was done to determine whether the lack of steroid exposure in the pass group had an impact on the results. No significant difference was found however between those on dexamethasone and those who were not exposed to steroids in the pass group for all the aforementioned variables. Additionally, after removing those who were not on steroids, a comparison of pass and fail groups showed that there was still a significant difference in duration and exposure. This strengthens the point that the groups are indeed different, independent of the lack of steroid exposure in the pass group.

The findings suggest a threshold point for failing an SST; once a person fails an SST at a particular point, it does not matter how much additional steroid exposure there is, they have already developed adrenal

RECOMMENDATIONS

It has been found that patients with solid brain tumours are more likely to develop adrenal insufficiency when on dexamethasone:

Dose: >2mg, Duration: >150 days , Exposure >450mgdays.

This demonstrates that patients on dexamethasone for >5 months or an exposure >450mgdays will almost certainly need hydrocortisone. These patients do not need an SST, they are at high risk of adrenal insufficiency and should therefore be [illegible]

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