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3 **To determine the efficacy of bilateral inferior petrosal sinus**
4 **sampling in differentiating Cushing disease from ectopic Cushing**
5 **syndrome**

6
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13
14 **Abstract**

15 Management of endogenous Cushing syndrome is based on its aetiology.
16 Increased Adrenocorticotrophic Hormone (ACTH) levels are the most common
17 cause of this disorder and, therefore, it is critical to determine the source of ACTH
18 before further management. Dynamic post contrast MRI is currently the most
19 common investigation implied to diagnose pituitary adenoma; however, it comes
20 with the drawback of low specificity and high false positive results.

21 Inferior petrosal sinus sampling (IPSS) is an established invasive procedure
22 performed to differentiate central versus peripheral source of ACTH which, in
23 turn, results in hypercortesolaemia. This is a series of 14 patients who underwent
24 IPSS at the Department of Radiology, Aga Khan University Hospital, Karachi,
25 from January 2006 to December 2018. The case series emphasises the role of
26 IPSS in the management of ACTH-dependent Cushing syndrome and combined
27 efficacy of Dynamic post-contrast MRI and the procedure under focus.

28 **Keywords:** Inferior petrosal sinus sampling, Cushing disease, Ectopic Cushing
29 syndrome, Hypercortesolemia.

30

31 **Introduction**

32 Adrenocorticotrophic hormone (ACTH) acts on the middle layer of adrenal cortex,
33 known as zona fasciculata, resulting in production of cortisol. Increased serum
34 ACTH levels, result in increased stimulation, which in turn results in
35 Hypercortisolaemia, broadly referred to as Cushing syndrome.⁽¹⁾

36 ACTH is produced by pituitary gland and hence a functional pituitary adenoma
37 can result in hyper secretion of ACTH, referred to as Cushing disease.^(2,3) Another
38 source for abnormal high serum levels of ACTH can be an Ectopic tissue, such
39 as a carcinoid tumour, in which case the spectrum is known as Ectopic Cushing
40 syndrome.^(4,5,6)

41 Determining the source is important, as it has therapeutic implications.^(7,8)

42 Dynamic MRI of the brain with contrast can reliably detect a pituitary adenoma;
43 however, literature reports low specificity and high false positive results
44 associated with this investigation. Moreover, prevalence of asymptomatic
45 pituitary adenomas in general population is potentially deceptive. In addition, it
46 has no role in identifying Ectopic source.^(9,10) Inferior petrosal sinus sampling

47 (IPSS) is an invasive procedure performed by an interventional radiologist to
48 determine the source of elevated serum ACTH.⁽¹¹⁾ With limited accuracy it can
49 also allow lateralisation of the pituitary adenoma within the pituitary gland.⁽¹²⁾

50 The common indications for performing IPSS include inconclusive MRI findings,
51 persistent high ACTH levels post-pituitary resection, discrepancy between
52 clinical, biochemical and imaging picture.^(13,14) Complications with BIPSS in
53 experienced hands are extremely rare. Most common complication is groin
54 haematoma. Other rare complications include a brainstem haemorrhage or non-
55 haemorrhagic brainstem infarction.^(15,16)

56 Pre-stimulation central to peripheral ACTH ratio of > 2 is suggestive of pituitary
57 adenoma, while a ratio of less than 2 is suggestive of ectopic source. Following
58 this, stimulation with Corticotrophin-releasing hormone or vasopressin is
59 performed. In case of pituitary adenoma post-stimulation central to peripheral
60 ratio would accentuate to 3:1 or more.⁽¹⁷⁾

61

62 **Case Report**

63 A 68-year-old female, who was a known case of diabetes mellitus and
64 hypertension, presented with a history of weight gain by 8 kg in the last 24
65 months, swelling on the feet and face, central obesity, easy bruisability, and
66 muscle weakness.

67 Her serum cortisol levels were 70 microg/dl (Normal reference range 3.4 – 22.4
68 microgram/ dl) and ACTH levels were 205 pg/ml (Normal reference range less
69 than 46 pg/ml)

70 She underwent Dynamic MRI of the brain with pituitary protocol which revealed
71 possibility of a questionable pituitary adenoma on the left side of the gland.
72 (Figure 1).

73 To solve the mystery, the patient subsequently underwent inferior petrosal sinus
74 sampling, results of which were suggestive of peripheral source of ACTH. (Table
75 1).

76 As a result, the patient underwent radiological surveillance; CT examination of
77 the chest showed a well-defined soft tissue density nodule in the left upper lobe;
78 however, this was too small to be characterised and hence follow up was
79 suggested. On six-month follow up CT examination of the chest, increase in size
80 of this nodule was noticed. PET CT scan was performed, which showed no
81 abnormal FDG uptake anywhere in the body. This nodule was excised and
82 histopathology revealed bronchial carcinoid. Subsequently, the patient's ACTH
83 levels went down and her symptoms improved.

84 In another case, a 36-year-old male presented with a history of generalised body
85 swelling and decreased vision. His serum ACTH and cortisol levels were
86 elevated. Subsequently, the patient underwent Dynamic contrast enhanced MRI
87 brain examination, (Figure 2) which revealed normal enhancement of the
88 pituitary gland with its normal contour. No area of differential non-enhancement
89 or focal bulge was seen. The study was negative for pituitary adenoma. For
90 further investigation, the patient underwent bilateral inferior petrosal sinus
91 sampling, the results of which were suggestive of a central source of ACTH with
92 left preponderance. (Table 2). Subsequently, surgery of the pituitary gland was
93 performed and histopathology confirmed the diagnosis of pituitary adenoma.

94

95 **Discussion**

96 We retrospectively reviewed our charts for patients who underwent inferior
97 petrosal sinus sampling at the Department of Radiology, Aga Khan University
98 Hospital, Karachi, from January 2006 till December 2018 with preliminary
99 diagnosis of ACTH-dependent Cushing syndrome. Our inclusion criteria was:
100 patients aged between 18-70 years; those who underwent BIPSS at our institute
101 during the study period; patients who, after or before the procedure, underwent
102 concomitant MRI or biopsy for analysis. Patients below the age of 18, patients
103 above the age of 70, patients who were lost to follow up and who did not have
104 MRI or histopathology available for comparison, and all those patients who had
105 sampling error or in whom adequate samples could not be collected were
106 excluded. In total, 23 patients underwent bilateral inferior petrosal sinus sampling
107 at our institute during the study period. One patient, a 13-year-old male, was
108 excluded because of age criteria. In one case adequate number of samples could
109 not be obtained, while seven cases had no MRI or histopathology correlation
110 available for comparison. Hence, the final cohort included 14 cases including 9
111 males and 5 females with mean age 40 +/- 14 standard deviation.

112 Each case in the final cohort had an MRI correlation available for comparison;
113 however, histopathology correlation was only available in 10 cases.

114 On 10 occasions, IPSS was suggestive of a central source while on four occasions
115 the results were conclusive for a peripheral source. Amongst the cases diagnosed
116 as central source on IPSS, seven were confirmed by MRI/Histopathology with a
117 pituitary adenoma, while amongst the cases labelled as peripheral source on IPSS,
118 a peripheral source was identified in only two cases, while in the other two MRI
119 was suggestive of a pituitary adenoma. (Table 3).

120 On the basis of this, two by two table, results were calculated and IPSS sensitivity
121 was found to be 77%, while specificity was 40%, positive predictive value (PPV)
122 70%, while negative predictive value was (NPV) 50%. The overall accuracy of
123 the procedure was found to be 64%. When the sample size was narrowed down
124 to those cases in which histopathology correlation was available, improvement in
125 all indicators (Table 4) with accuracy of the procedure increasing to 89% was
126 observed. Both inferior petrosal sinus sampling and MRI were concordant for
127 central source of ACTH in six cases. In 4/6 cases (66 %) inferior petrosal sinus
128 sampling was able to localise pituitary adenoma accurately. No complication was
129 encountered in the 23 procedures performed with the only drawback being
130 inconclusive sample in one patient. A decreasing trend in requests for inferior
131 petrosal sinus sampling was observed at our centre. The major factors associated
132 with this observation are invasive nature of the procedure, cost associated with
133 the procedure and installation of 3 tesla MRI scanner at our institute, resulting in
134 better image resolution. Compared to international standard technique, an MRV
135 is not performed prior to every procedure and 4 Fr H1 catheters are used instead
136 of 2.7 Fr micro catheters. This approach helps us reduce the cost of procedure
137 without much impact on the quality of samples. Inferior petrosal sinus sampling
138 is an established technique used to distinguish central versus peripheral source of
139 abnormal ACTH production with rare reported complications.⁽¹⁸⁾ It is generally

140 considered safe. In our cohort, only one complication was observed, which was
141 inadequate sampling, with no major complication.

142 Sensitivity and specificity calculated in our study is low compared to the
143 literature.^(19, 20) However, in 10 cases from our cohort, with available
144 histopathology correlation, IPSS made the wrong call on only one occasion,
145 which points out to the reliability of the test. Hence, this can be assumed that non-
146 availability of histopathology correlation in the rest of the cases may have
147 impacted our results. Amongst the cases where both MRI and IPSS were positive
148 for pituitary adenoma, none of them turned out to be negative at histopathology,
149 suggesting high combined accuracy of both the procedures when performed
150 together.

151 Inferior petrosal sinus sampling can help detect a peripheral source, which might
152 otherwise go undiagnosed.⁽²¹⁾ In our cohort, two cases were eventually diagnosed
153 as bronchial carcinoids, in which IPSS had detected a peripheral source. Although
154 our results are not recommending it as a gold standard, however, if performed in
155 conjugation with Dynamic post contrast MRI, it can improve the diagnostic
156 reliability as well as prevent false positive results.

157

158 **Conclusion**

159 Inferior petrosal sinus sampling (IPSS) is a reliable and safe invasive procedure
160 which can help differentiate Cushing disease from Ectopic Cushing syndrome,
161 along with high combined accuracy of IPSS and MRI brain pituitary protocol.
162 This test can be a useful tool in cases where diagnosis is difficult.

163

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168

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Table 1: Inferior petrosal sinus sampling results in patient 1.

	RIGHT PETROSAL SINUS	LEFT PETROSAL SINUS	PERIPHERAL BLOOD
BASAL	220 pg/ml	253pg/ml	237pg/ml
5 MIN POST VASOPRESSIN	231 pg/ml	297 pg/ml	186 pg/ml
10 MIN POST VASOPRESSIN	190 pg/ml	323 pg/ml	247 pg/ml

243 **Picogram / millilitre = pg/ml**

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Table 2: Inferior petrosal sinus sampling results in patient 2

	RIGHT PETROSAL SINUS	LEFT PETROSAL SINUS	PERIPHERAL BLOOD
BASAL PRESTIMULATION			52 pg/ml

5 MIN POST STIMULATION	191 pg/ml	691 pg/ml	64 pg/ml
10 MIN POST STIMULATION	262 pg/ml	887 pg / ml	158 pg/ml

248 **Picogram / millilitre = pg/ml**

249

250 -----

251

252 **Table 3: 2 x 2 table**

	Histopathology/MRI		
	Positive	Negative	total
IPSS	7	3	10
	2	2	4

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254 -----

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256 **Table 4: Results in patients with histopathology correlation**

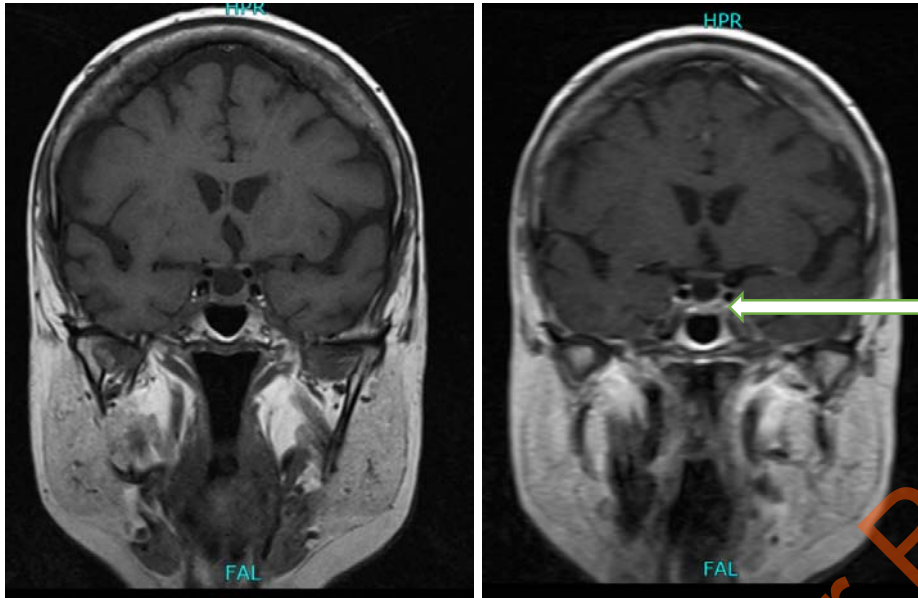
INDICATOR	VALUE IN PERCENTAGE
Sensitivity	100 %
Specificity	66.6 %
Positive Predictive Value	85.7 %
Negative Predictive Value	100%
Accuracy	89 %

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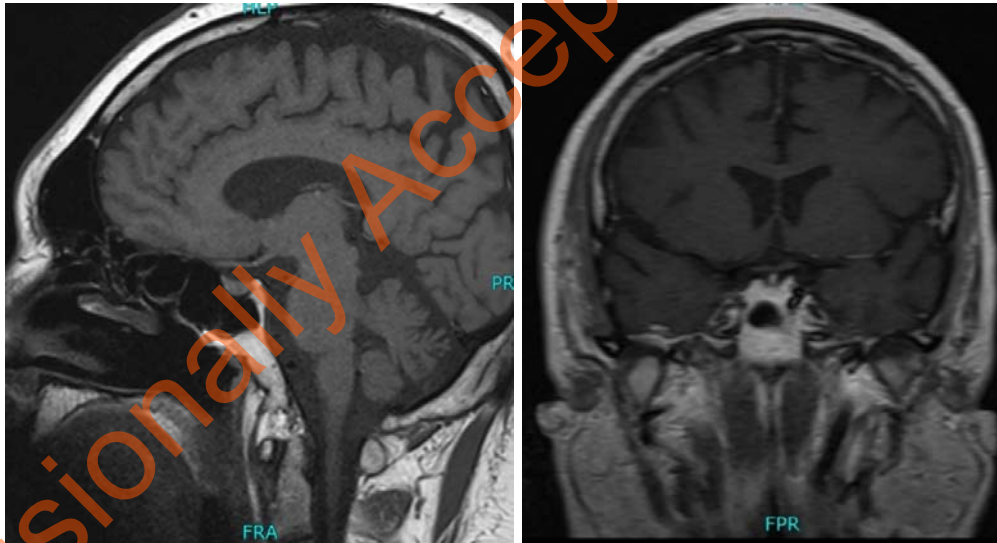
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 261 **Figure 1: Coronal T1 pre-contrast image on the left side and dynamic post**
 262 **contrast coronal image on the right side, showing a small area of differential**
 263 **non-enhancement (arrow) in the left side of pituitary gland without any**
 264 **bulge of asymmetry.**

265
 266
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268
 269 **Figure 2. 1 and 2. 2 T1 sagittal and Post-contrast Coronal images at the level**
 270 **of sella turcica reveal normal contour of the pituitary gland without any**
 271 **focal area of differential non enhancement or bulge. No imaging evidence to**
 272 **suggest pituitary adenoma.**

273