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Radiological and clinical biomarkers in patients with central post stroke pain

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ABSTRACT

Background: Central post-stroke pain (CPSP) occurs following cerebrovascular accidents and is a neuropathic pain syndrome that is characterized by stimulation-independent pain; shooting, burning, or electric shock-like sensation and paresthesia. Multiple pathogenetic theories have been proposed for the CPSP including disinhibition, central sensitization, thalamic changes, and altered function of spinothalamic tract (STT). Investigations such as MRI DTI can help to understand the pathogenesis of CPSP.

Objective: To determine the radiological and clinical biomarkers in cases with CPSP.

Methods: This case-control study was retrospectively conducted upon 60 persons divided into 20 CPSP cases (group 1), 20 cases with no CPSP (group 2) and 20 healthy controls (group 3). All subjects had Routine MRI and complete neurological examination including "Sensory testing but stroke patients were evaluated by quantitative assessment of neuropathic pain, the National Institutes of Health Stroke Scale (NIHSS), Ashworth scale, Modified Rankin Scale (MRS) and Hamilton depression rating scale (HAM-D scale).

Results: Significant differences existed among studied groups as regard motor examination, sensory examination, NIHSS score and Hamilton depression score. A non-significant difference was detected among the groups regarding MRS findings. A significant difference existed between groups 1 and 2, between groups 1 and 3 while no significant difference was detected between groups 2 and 3 for all FA readings and all ADC readings in ipsilateral affected side assessed at internal capsule, midbrain, and pons. No significant difference existed between groups 1 and 2, between groups 1 and 3 and between groups 2 and 3 as regard FA readings and ADC readings in contralateral side assessed at internal capsule, midbrain, and pons.

Conclusion: Our study highlighted the significance of white matter tracts (WMT) other than the conventional pain pathways in CPSP and can thus serve as a predictive marker for CPSP onset or a prognostic marker after any drug therapy or neuromodulatory treatment.

Keywords: Central Post Stroke Pain, Modified Rankin Scale, Hamilton depression rating scale, Diffusion Tensor Tractography, Diffusion Tensor Imaging.

INTRODUCTION

Stroke is the 2nd most common cause of death **[1]**. Stroke survivors may develop several complications which include depressive disorder, physical disabilities, cognitive deficits and post-stroke pain (PSP) **[2]**. The prevalence of PSP in published studies is variable, but a large study in the united states demonstrated that > 50% of general population developed pain the previous three months **[3]**.

The prevalence of PSP is 11–66% **[4]**. PSP has different forms such as headaches, pain in shoulders, pain because of muscle stiffness, spasms, complex regional pain syndrome and CPSP **[5]**. Risk factors of PSP include sex (females are more affected), old age, consumption of alcoholic drinks, and depression. On the other hand, ischaemic stroke, spasticity, decreased upper limb movement as well as sensory dysfunction are among the stroke-related risk factors of PSP **[4]**.

CPSP is a neuropathic pain syndrome that occurs post-stroke. It is characterized by stimulation-independent pain; shooting, lancinating, burning, electric shock-like sensations; and paresthesia **[6]**. About 8–14% of stroke patients develop CPSP **[7]**. Multiple pathogenetic theories have been proposed for the CPSP. These include central sensitization, abnormal neural excitability by disinhibition, altered STT function, thalamic alterations, and inflammatory processes of neural tracts. Furthermore, several brain structures have been suggested to have roles in the pathogenetic process of CPSP such as cingulate gyrus, somatosensory cortices, lateral thalamus, STT, and medial lemniscus **[8-10]**.

Diffusion tensor tractography (DTT) and diffusion tensor imaging (DTI) provide 3D imagining and estimation of STT **[11]**. Several reports using DTT and DTI, revealed that STT injury is the pathogenetic mechanism of CPSP after intracerebral haemorrhage and traumatic brain injuries **[12-14]**. So, we did study to determine radiological and clinical biomarkers in CPSP individuals.

SUBJECTS AND METHODS

This retrospective case-control study enrolled 60 subjects including 40 patients with stroke attending Mansoura University hospitals outpatient clinic and 20 healthy controls. Patients were selected randomly in the period from February 2022 to February 2023. The 40 patients with stroke were allocated into 2 groups, each group had 20 patients, first group included patients with CPSP while second group had stroke patients with no CPSP.

This study included patients aged above 18 years from both sexes, diagnosed with cerebrovascular stroke by CT brain scan or MRI brain for at least one month after onset and CPSP cases were included with a score ≥ 4 on a 10-point visual analog scale (VAS). But we excluded individuals who refused participation, those having severe cognitive or communication deficits or patients with score ≤3 on a 10-point VAS. The healthy control group included matched subjects aged above 18 years from both sexes with no previous history of central nervous system disease.

Methods

Each participant was subjected to thorough history taking including history of previous TIA or stroke and related risk factors. Complete neurological examination included “Sensory

testing" of the normal side, and then the abnormal sides were tested. Testing for pinprick and touch was also performed. Cold metal rod for temperature testing, and a 128-Hz tuning fork for vibration were utilized. Joint position sense underwent testing in toes and fingers. Laboratory investigations included CBC, INR, liver function test, and serum creatinine. Radiological examination included routine MRI.

MRI techniques included T1 axial whole brain, T2 axial whole brain, T2 coronal whole brain, T1 sagittal whole brain and DWI "diffusion-weighted imaging" whole brain axial, DTI "Diffusion tensor imaging" whole brain axial and SWI "susceptibility weighted imaging" axial whole brain.

A single-shot echo planer imaging sequence (TR/TE 3200 /90 ms) with parallel imaging (sensitivity Encoding [sense] reduction factor p) was utilized to obtain DTI data. Diffusion gradients were applied along 32 axes, utilizing a b-value of 0 and 1000 s/mm2. A field of view of 224×224 mm2 and a data matrix of 92×88 were utilized, to obtain voxel dimensions of 2.43×2.54×2.5 mm3. A total of 48 slices with 2.5 mm thickness and no gap were obtained. The scan necessitated approximately 7 - 8 min.

Post Processing

An Expert radiologist determined the specific anatomic locations of seed and target regions of interest of the STT at post part of pons and midbrain and superior thalamic radiation (STR) at posterior limb of internal capsule. Then measured normalized fractional anisotropy (FA) and mean diffusivity (MD) values of the STT and STR.

Detection of CPSP by applying the Diagnostic criteria for CPSP **[15]** which included 1. Exclusion of other common pain causes, 2. pain with a special neuroanatomically-apparent distribution: Either confined to one body side and/or one face side or one on one body side with involvement of the contralateral face side, 3. history of stroke: Sudden neurologic symptoms with pain onset at or following stroke, 4. signs of a special neuroanatomically apparent distribution by neurologic assessment: Prediction of negative or positive sensory signs in the pain area, unprompted and/or evoked pain localized within a branch of sensory abnormality, and neuroanatomically-apparent distribution of sensory dysfunction and 5. pointing to relevant vascular lesion in CT or MR brain. If criteria 1, 2, and 3 were met, a possible CPSP was diagnosed. If criteria 1, 2, and 3 together with either criteria 4 or 5 were me, probable CPSP was diagnosed . Definite CPSP was diagnosed if all criteria were met.

Also, every patient was subjected to quantitative evaluation of neuropathic pain by using the Short-form McGill Pain Questionnaire (SF-MPQ) which was utilized to assess the severity of CPSP. This questionnaire includes 3 items: pain rating index, pain intensity, and VAS.

Evaluation of the severity of neurological deficits by using the NIHSS, evaluation of spasticity using modified Ashworth's scale, evaluation of disability using MRS, and evaluation of the severity of depression by the HAM-D scale were done to every patient.

Statistical Analysis

Data were analysed using SPSS, V 25 (SPSS Inc., PASW statistics for windows. Chicago: SPSS Inc.). Qualitative data were expressed as frequencies and percents. Quantitative data were expressed as means± SDs for normally distributed data after testing normality by Kolmogrov-Smirnov test. Significance was set at (≤0.05) level. Chi-Square, Fisher exact test,

Monte Carlo tests were utilized to compare qualitative data among the groups. Student t-test was utilized to compare 2 independent groups for normally distributed data. One Way ANOVA test was compared > 2 independent groups with Post Hoc Tukey test to detect pair-wise comparison. The validity (sensitivity and specificity) and the best cut-off value was calculated using receiver operating characteristics curve.

RESULTS

This case-control study included 60 subjects as follows: 20 stroke cases with CPSP, 20 stroke cases with no CPSP and 20 healthy control subjects. Table **(1)** demonstrates no significant difference among groups as regards mean age and sex. Smokers represent by 40% of group 1and 2 & 15% of group 3. Positive past history was detected among 85% of group 1, 80% of group 2 and 20% of group 3. A significant difference exists among the groups as regards motor examination with (abnormal) motor examination was detected among 95% of group 1, 100% of group 2 & none of group 3. A significant difference exists among groups regarding sensory examination. For group1; 50% Left hemihypothesia, 30% Right hemihypothesia, 15% Left hemihypothesia including face and 5% Right hemihypothesia including face and for group 2; 65% no abnormality detected, 30% Left hemihypothesia and 5% Right hemihypothesia including face. For group 3; all cases have normal examination.

Table (1): Demographic characteristics, past history, motor and sensory examination between the studies groups

	G 1	**G 2**	**G 3**	**Test of significance**	**Within group significance**
Age / years	59.20±9.41	57.20±8.56	53.65±7.15	F=2.23 P=0.117	P1=0.456 P2=0.06 P3=0.188
Sex Males Females	 15(75.0) 5(25)	 15(75.0) 5(25.0)	 14(70.0) 6(30.0)	χ^2=0.170 p=0.918	P1=1.0 P2=0.723 P3=0.723
Special habits Non smoker Ex smokers Smokers	 8(40.0) 4(20.0) 8(40.0)	 11(55.0) 1(5.0) 8(40.0)	 16(80.0) 1(5.0) 3(15.0)	=8.43 p=0.08	 p1=0.321 p2=0.034* p3=0.202
Past history -ve +ve	 3(15.0) 17(85.0)	 4(20.0) 16(80.0)	 16(80.0) 4(20.0)	χ^2=22.14 p<0.001*	p1=0.677 p2=0.001* p3=0.001*
Abnormal motor examination -ve +ve	 1(5.0) 19(95.0)	 0 20(100)	 20(100.0) 0(0.0)	5.82 p<0.001*	p1=1.0 p2<0.001* p3<0.001*
Sensory examination NAD Right hemihypothesia Left hemihypothesia Left hemihypothesia including face Right hemihypothesia including face	 0(0.0) 6(30) 10(50) 3(15) 1(5)	 13(65) 0 6(30) 0 1(5)	 20(100) 0 0 0 0	7.23 p<0.001*	 p1<0.001* p2<0.001* p3=0.014*

F:One Way ANOVA test , χ^2=Chi-Suare test , *statistically significant , p1: difference between groups 1& 2 , p2: difference between groups 1& 3 , p3: difference between groups 2& 3

Table **(2)** illustrates that 40% of the studied cases in group 1 have dull aching short form MC Gill plain pain type, 40% throbbing pain and 20% burning pain. VAS score is distributed as following; 40% score 5, 25% score 6, 20% score 8 and 15% score 7. Other classification demonstrates that 60% of the cases have distressing pain, 25% discomforting pain and 15% horrible pain.

Table (2): Pain results of the studied patients with CPSP

G 1	n	%
short form MC Gill plain type		
throbbing	8	40.0
burning	4	20.0
dull aching	8	40.0
VAS score		
5	8	40.0
6	5	25.0
7	3	15.0
8	4	20.0
Discomforting	5	25.0
Distressing	12	60.0
Horrible	3	15.0

Table **(3)** demonstrates a significant difference between the study groups in terms of NIHSS score and Hamilton depression score, all cases in group 2 have NIHSS score 0 versus group 1 have NIHSS score distribution as following; 45% NIHSS 1, 30% NIHSS 2, 10% NIHSS 3, 10% NIHSS 4 AND 5% NIHSS 5. Group 1 shows mean higher Hamilton depression score compared to group 2. For group 2; 75% of cases have Modified ASHWORTH scale 0, 15% score 2, 55 score 1 and 5% score 3. No significant difference existed between studied groups as regards MRS findings. For group 1; 35%score 2, 30% score 1, 20% score 3, 10% score 0 and 5% score 4. For group 2; 35% score 3, 30% score 1, 20% score 0, 14% score 3 and 0% score 4.

Table (3): Comparison of NIHSS, Modified ASTHWORTH scale, Hamilton scale and **MRS** between groups 1& 2

	G 1 N(%)	G 2 N(%)	Test of significance
NIHSS			
0	0(0.0)	20(100.0)	MC=40.0
1	9(45.0)	0	p<0.001*
2	6(30.0)	0	
3	2(10.0)	0	
4	2(10.0)	0	
5	1(5.0)	0	
Modified ASHWORTH scale			
0	20(100.0)	15(75.0)	MC=5.71

1 2 3	0 0 0	1(5.0) 3(15.0) 1(5.0)	P=0.126
Hamilton depression	7.05±3.93	3.84±2.34	z=3.07 p=0.004*
MRS 0 1 2 3 4	 2(10.0) 6(30.0) 7(35.0) 4(20.0) 1(5.0)	 4(20.0) 6(30.0) 7(35.0) 3(15.0) 0	 MC=1.81 p=0.771

Z: Mann Whitney U test MC: Monte Carlo test, *statistically significant, p1: difference between groups 1& 2, p2: difference between groups 1& 3, p3: difference between groups 2& 3

Table **(4)** illustrates significant difference between groups 1 &2, between groups 1&3 while no significant difference is detected between groups 2&3 for all FA readings in ipsilateral affected side assessed at internal capsule, midbrain and pons. Mean FA is higher among group 3 followed by group 2 and group 1, respectively. No significant difference exists between groups 1 and 2, between groups 1and 3 and between groups 2 and 3 as regard FA readings in Contralateral side assessed at internal capsule, midbrain and pons.

Table (4): Comparison of FA for the ipsilateral and contralateral side between studied groups

ipsilateral side	**G 1**	**G2**	**G 3**	**Test of significance**	**P- value**
internal capsule FA1	0.609±0.11	0.696 ±0.06	0.738±0.04	F=14.04 P<0.001*	P1=0.001* P2=0.001* P3=0.08
internal capsule FA2	0.627±0.13	0.698±0.056	0.735±0.03	F=[illegible]5 P<0.001*	P1=0.008* P2=0.001* P3=0.167
Pons Fa	0.531±0.151	0.632±0.088	0.696±0.07	F=[illegible]75 P<0.001*	P1=0.005* P2=0.001* P3=0.07
Midbrain Fa	0.619±0.130	0.690±0.096	0.731±0.065	[illegible]6.40 P<0.003*	P1=0.029* P2=0.001* P3=0.201
Contralateral side					
internal capsule FA1	0.698±0.073	0.689±0.054	0.712±0.04	F=0.738 P=0.482	P1=0.600 P2=0.497 P3=0.231
internal capsule FA2	0.731±0.107	0.712±0.061	0.714±0.053	F=0.384 P=0.683	P1=0.423 P2=0.487 P3=0.914
Pons Fa	0.635±0.13	0.657±0.097	0.696±0.07	F=1.88 P=0.162	P1=0.789 P2=0.061 P3=0.224
Midbrain Fa	0.697±0.16	0.683±0.129	0.739±0.051	F=1.11 P=0.335	P1=0.703 P2=0.295 P3=0.155

F:One Way ANOVA test, *statistically significant, p1: difference between groups 1& 2, p2: difference between groups 1& 3, p3: difference between groups 2& 3

Table **(5)** demonstrates significant difference among groups 1 and 2, among group 1 & 3 whereas a non-significant difference existed between groups 2 and 3 for all ADC readings in ipsilateral affected side assessed at internal capsule, midbrain, and pons. Mean ADC was lower among group 3 followed by group 2 and group 1, respectively. A non-significant difference exists between groups 1 and 2, between groups 1 and 3 and between groups 2 and 3 as regard ADC readings in contralateral side assessed at internal capsule, midbrain, and pons.

Table (5): Comparison of ADC for the ipsilateral and contralateral side between studied groups

Ipsilateral side	**G 1**	**G2**	**G3**	**Test of significance**	**P- value**
internal capsule ADC1	0.770±0.05	0.732±0.06	0.737±0.02	F=3.85 P=0.027*	P1=0.013* P2=0.03* P3=0.728
internal capsule ADC2	0.776±0.05	0.729±0.041	0.734±0.036	F=[illegible]0 P=0.001*	P1=0.001* P2=0.002* P3=0.763
Pons ADC	0.730±0.16	0.632±0.102	0.639±0.112	F=3.74 P=0.03*	P1=0.017* P2=0.026* P3=0.864
Midbrain ADC	0.796±0.104	0.644±0.244	0.553±0.205	F=8.06 P=0.001*	P1=0.016* P2<0.001* P3=0.142
Contralateral side					
Internal capsule ADC1	0.731±0.068	0.730±0.03	0.714±0.053	F=0.657 P=0.522	P1=0.971 P2=0.316 P3=0.334
Internal capsule ADC2	0.719±0.15	0.725±0.04	0.732±0.024	F=0.88 P=0.915	P1=0.846 P2=0.675 P3=0.822
Pons ADC	0.756±0.06	0.735±0.049	0.746±0.023	F=0.894 P=0.415	P1=0.187 P2=0.534 P3=0.481
Midbrain ADC	0.764±0.08	0.704±0.210	0.744±0.051	F=1.09 P=0.343	P1=0.152 P2=0.619 P3=0.344

F:One Way ANOVA test, *statistically significant, p1: difference between groups 1and 2, p2: difference between groups 1and 3, p3: difference between groups 2 and 3

Table **(6)** demonstrates that area under curve for FA assessed at internal capsule, pons and midbrain is good in differentiating between group 1 &2 with the best detected cut off point from the curve 0.694 for internal capsule FA1 yielding sensitivity 80% and specificity 60%, 0.691 for internal capsule FA2 yielding sensitivity 60% and specificity 55%, 0.594 for pons Fa yielding sensitivity 75% and specificity 85%, 0.687 for Midbrain Fa yielding sensitivity

70% and specificity 60%. Table **(7)** shows that area under curve for FA assessed at internal capsule, pons and midbrain is good to excellent in differentiating between group 1 &3 with the best detected cut off point from the curve 0.689 for internal capsule FA1 yielding sensitivity 80% and specificity 90%, 0.7265 for internal capsule FA2 yielding sensitivity 70% and specificity 80%, 0.647 for pons Fa yielding sensitivity 80% and specificity 75%, 0.694 for Midbrain Fa yielding sensitivity 70% and specificity 85%. Table **(8)** illustrates that area under curve for ADC assessed at internal capsule, pons and midbrain is good to excellent in differentiating between group 1 &2 with the best detected cut off point from the curve 0.734 for internal capsule FA1 yielding sensitivity 80% and specificity 55%, 0.744 for internal capsule FA2 yielding sensitivity 75% and specificity 75%, 0.693 for pons Fa yielding sensitivity 90% and specificity 85%, 0.749 for Midbrain Fa yielding sensitivity 65% and specificity 70%.

Table (6): Validity of FA on ipsilateral side between group 1&2

	Ipsilateral side	AUC (95%CI)	P- value	Cut-off value	Sensitivity %	Specificity %
Between group 1&2	internal capsule FA1	0.745 (0.592-0.898)	0.008*	0.694	80.0	60.0
	internal capsule FA2	0.634 (0.458-0.810)	0.148	0.691	60.0	55.0
	Pons Fa	0.726 (0.556-0.897)	0.014*	0.594	75.0	85.0
	Midbrain Fa	0.709 (0.454-0.873)	0.024*	0.687	70.0	60.0

AUC: Area under curve

Table (7): Validity of FA on ipsilateral in differentiating between group 1 & 3

	Ipsilateral side	AUC (95%CI)	P- value	Cut-off value	Sensitivity %	Specificity %
Between group 1&3	internal capsule FA1	0.880 (0.773-0.987)	<0.001*	0.6895	80.0	90.0
	internal capsule FA2	0.770 (0.615-0.925)	0.003*	0.7265	70.0	80.0
	Pons Fa	0.842 (0.714-0.971)	<0.001*	0.647	80.0	75.0
	Midbrain Fa	0.796 (0.655-0.937)	0.001*	0.694	70.0	85.0

AUC: Area under curve

Table (8): Comparison of ADC on the ipsilateral side between group 1 & 2

	Ipsilateral side	AUC (95%CI)	P-value	Cut-off value	Sensitivity %	Specificity %
Between	Internal capsule ADC1	0.714 (0.554-0.874)	0.02*	0.7335	80.0	55.0

	Internal capsule ADC2	0.769 (0.618-0.919)	0.004*	0.744	75.0	75.0
	Pons ADC	0.819 (0.665-0.973)	0.001*	0.693	90.0	85.0
	Midbrain ADC	0.677 (0.503-0.852)	0.055	0.749	65.0	70.0

AUC: Area under curve

DISCUSSION

CPSP occurs after stroke when the lesion causes damage of the somatosensory system. This type of pain has central origin and cannot be attributed to peripheral origin **[16].** Many theories have been proposed regarding the pathogenesis of CPSP, including the medial pain system, which is a component of affective and motivational pain transmitted by the medial STT and the lateral pain system, which is a sensory component and pain discrimination transmitted by the lateral STT **[17].**

According to the central sensitization theory, neuronal hyperexcitability and loss of facilitation can result from CNS lesions. In the disinhibition theory, there is an imbalance of the interaction of brainstem nuclei, spinal cord, and thalamo-cortical circuit **[18].** Other theories include changes in STT's plasticity as revealed by functional MRI, increased thalamic activity as a result of the increase in burst activity of firing neurons in the thalamic somatosensory nucleus, as well as the dynamic reverberation theory that suggests an imbalance of the oscillatory pattern in the thalamo-cortical circuits **[19].**

So, this study aimed at to determination of the radiological and clinical biomarkers in cases with CPSP. Our study included 60 patients; 20 CPSP cases (group 1), 20 stroke cases with no CPSP (group 2) and 20 healthy controls (group 3). No significant difference is detected among the groups in terms of age and sex. Sex distribution was as following; 75% of group 1, 2 and 70% for group 3 were males. Positive past history "hypertension, diabetes mellitus" was detected among 85% of group 1, 80% of group 2 and 20% of group 3. In harmony, **Porey et al. [19]** evaluated 24 cases with both ischaemic and haemorrhagic strokes, using MRI with DTI acquisition. The mean age was 62.54 ± 9.71 years; with males represented 54.1% of cases and females represented 45.8% of cases.

In our study, a significant difference existed among the groups regarding motor examination with abnormal motor examination detected among 95% of group 1, 100% of group 2 & none of group 3. A significant difference existed among study groups in terms of sensory examination. For group 1; 50% Left hemihypothesia, 30% Right hemihypothesia, 15% Left hemihypothesia including face and 5% Right hemihypothesia including face and for group 2; 65% normal sensory examation, 30% Left hemihypothesia and 5% Right hemihypothesia including face. For group 3; all cases have normal sensory examination. **Porey et al. [19]** evaluated CPSP in 11 cases with ischaemic strokes and in 13 cases with haemorrhagic strokes. CPSP was Right side in (70.8%) and in Left side (29.1%).

The current study illustrated that 40% of the studied cases in group1 had dull aching, 40% throbbing pain and 20% burning pain. VAS score was distributed as following; 40% score 5, 25% score 6, 20% score 8 and 15% score 7. Other classification demonstrated that 60% of the

cases had distressing pain, 25% discomforting pain and 15% horrible pain. **de Oliveira et al. [20]** evaluated 40 CPSP cases that underwent a standardized sensory-motor neurologic evaluation. Median pain intensity according to VAS was 10. The commonest pain types were burning (70%) and electrical shock-like sensations (22.5%).

This study showed no significant difference among the study groups regarding MRS findings. For group 1; 35% score 2, 30% score 1, 20% score 3, 10% score 0 and 5% score 4. For group 2; 35% score 3, 30% score 1, 20% score 0, 14% score 3 and 0% score 4. Our study demonstrated significant difference among the groups in terms of NIHSS score and Hamilton depression score. All cases in group 2 had NIHSS score 0 versus group 1 had NIHSS score distribution as following; 45% NIHSS 1, 30% NIHSS 2, 10% NIHSS 3, 10% NIHSS 4 and 5% NIHSS 5, which can be explained partially by that All patients of Group 2 had hemihypothesia.

Mean higher Hamilton depression score was detected in group 1 versus group 2. For group 2; 75% of cases had Modified ASHWORTH scale 0, 15% score 2, 55 score 1 and 5% score 3. **de Oliveira et al. [20]** found that in CPSP cases, the mean pain duration (5.73 years), pain scores, and depression rates, were increased. This indicated high chronicity, psychosocial stress and refractoriness to therapy.

Our study illustrated significant difference among groups 1 and 2, between groups 1 and 3 while no significant difference was detected between groups 2 and 3 for all FA readings in ipsilateral affected side assessed at internal capsule, midbrain, and pons. Mean FA was higher among group 3 followed by group 2 and group 1, respectively. Also, a non-significant difference existed between groups 1 and 2, between groups 1 and 3 and between groups 2 and 3 as regard FA readings in contralateral side assessed at internal capsule, midbrain, and pons.

Notably, decreased FA and high ADC or RD are associated with demyelination, axonal degeneration, or disturbed connections **[21].** Consistent with our findings, **Park et al. [22]** studied 3 groups: 17 stroke cases with CPSP; 26 stroke cases with no CPSP and 34 healthy controls. They reported lower FA value of STT and STR among CPSP cases compared with values in stroke cases with no CPSP and in control group.

To detect the prevalence of CPSP, **Hong et al. [23]** studied 34 cases with intact STT and 18 cases with injured STT in haemorrhagic stroke. The prevalence was greater among patients with preserved STT. CPSP and non-CPSP subgroups had lower FA values and higher MD values of STT than controls.

Our study demonstrated significant difference between groups 1 and 2, between groups 1 and 3 while no significant difference existed between groups 2 and 3 for all ADC readings in ipsilateral affected side assessed at internal capsule, midbrain and pons. Mean ADC was lower among group 3 followed by group 2 and group 1, respectively. Our work illustrated no significant difference among the study groups regarding ADC readings in contralateral side assessed at internal capsule, midbrain and pons.

On the other hand, **Porey et al. [19]** found higher ADC value in BG, STR, CST, and SSC on comparison normal versus lesion sides. Also, ischaemic strokes showed significant alterations in ADC values of STR and CST, whereas haemorrhagic strokes showed significant ADC value alterations of STR and SSC.

Our study demonstrated that area under curve for FA assessed at internal capsule, pons and midbrain was good in differentiating between group 1 &2 with the best detected cut off point from the curve 0.694 for internal capsule FA1 yielding sensitivity 80% and specificity 60%, 0.691 for internal capsule FA2 yielding sensitivity 60% and specificity 55%, 0.594 for pons Fa yielding sensitivity 75% and specificity 85%, 0.687 for Midbrain Fa yielding sensitivity 70% and specificity 60%. While in differentiating between group 1 & 3, the area under curve for FA assessed at internal capsule, pons and midbrain was good to excellent with the best detected cut off point from the curve 0.689 for internal capsule FA1 yielding sensitivity 80% and specificity 90%, 0.7265 for internal capsule FA2 yielding sensitivity 70% and specificity 80%, 0.647 for pons Fa yielding sensitivity 80% and specificity 75%, 0.694 for Midbrain Fa yielding sensitivity 70% and specificity 85%.

The current study illustrated that area under curve for ADC assessed at internal capsule, pons and midbrain was good to excellent in differentiating between group 1 & 2 with the best detected cut off point from the curve 0.734 for internal capsule FA1 yielding sensitivity 80% and specificity 55% , 0.744 for internal capsule FA2 yielding sensitivity 75% and specificity 75%, 0.693 for pons Fa yielding sensitivity 90% and specificity 85%, 0.749 for Midbrain Fa yielding sensitivity 65% and specificity 70%.

In the study by **Sundgren and co-workers [24],** the structures of the primary and secondary somatosensory cortices, the insula, the anterior cingulate, the thalamus, the dorsal lateral prefrontal cortex and the basal ganglia were referred to as “pain matrix” in their study on fibromyalgia cases. DTI of thalamic fibers has been utilized for monitoring of changes prior to and following deep brain stimulation of ventral posterolateral nucleus in chronic pain **[25]. Moura et al. [26]** stated that FA measured at an early phase post-stroke predicted motor recovery. In ischaemic stroke cases, **Werring et al. [27]** found that low FA had an association with cerebral infarction in corticospinal tract remote from the lesion. The discrepancies in findings of the previous studies can be explained by many factors such as differences in the subjective nature of pain, the cause of stroke, different populations, selection criteria and small sample size.

CONCLUSION

The current study signifies the importance of WMT other than the conventional pain pathways in CPSP and can serve as a predictive marker of CPSP onset or a prognostic marker after any drug therapy or neuromodulatory treatment.

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