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# *Clinico-radiologic profile of patients with Idiopathic Intracerebral Calcifications: Differentiation between Fahr's Syndrome and Fahr's Disease.*

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**ABSTRACT**

***Background:*** *Intracerebral calcification is an unusual degenerative disorder characterized by accumulation of calcium in basal ganglia and other intracerebral sites. The calcifications are usually found in the basal ganglia including caudate nucleus, putamen and globus pallidus.*

***Aims and Objectives:*** *Describing clinical profile of patients with intracerebral calcifications and also to identify differences in clinic-radiologic manifestations between patients with Fahr's disease and Fahr's syndrome.*

***Material and Methods:*** *We enrolled 22 patients with intracerebral calcifications after obtaining informed consent. These patients were evaluated by history taking, clinical examination and laboratory investigations. The investigations included complete blood counts, liver function tests, kidney function tests, serum calcium level, serum phosphate, serum parathromone, serum vitamin D and thyroid profile. Patients with disorders of calcium metabolism were classified as Fahr's syndrome and those without such disorders were classified as Fahr's disease. Various clinical and radiological features were compared between the two groups.*

***Results:*** *We identified 22 patients with intracerebral calcifications. 3 (59.1%) patients were females, and nine (40.9%) patients were male. Mean [Standard Deviation (SD)] age of these patients was 40.7 (8.1) years (range 25 – 56 years). Median duration of symptoms was 6 years (range 3 months – 11 years). The clinical manifestations were pure psychiatric in 6 (27.3%); pure neurological in 5 (22.7%) and mixed in 11 (50%) patients. The frequencies of various psychiatric presentations were: psychosis in 10 (45.5%) patients; neurosis in 9 (40.9%) patients; mood disorders in 10 (45.5%) patients [which included five patients with mania and five patients with depression]. Neurological presentations were: seizures in 8 (36.4%); extrapyramidal features in 10 (45.5%) patients [which included rigidity, bradykinesia, dystonia and tremors; pyramidal features in 7 (31.8%) patients; and cerebellar symptoms in five (22.7%) patients. The distribution of intracerebral calcification was as follows: caudate nucleus in 22 (100%) patients; putamen 22 (100%); globus pallidus in 22 (100%); cerebellum in 22 (100%); thalamus in 11 (50%) patients; subcortical in 10 (45.5%); and lobar in three (13.6%) patients. 6 out of 22 patients had Fahr's Syndrome and 16 out of 22 patients had fahr's Disease. There was no statistically significant difference between clinical and radiologic features between two groups.*

***Conclusions:*** *The common sites of intracerebral calcification in these disorders include basal ganglia, thalamus, cerebellum and cerebrum. The clinical presentations include psychiatric manifestations and neurological features including seizures and extrapyramidal symptoms. There are no significant clinical and radiological differences between patients with Fahr's syndrome and Fahr's disease.*

**Keywords:** *Neuropsychiatric manifestations*

## INTRODUCTION

*Intracerebral calcification is an unusual degenerative disorder characterized by accumulation of calcium in basal ganglia and other intracerebral sites. The calcifications are usually found in the basal ganglia including caudate nucleus, putamen and globus pallidus [1,2,3]. However, it has also been noted at the non-basal ganglia sites as well [4]. This pathology has been linked to multitudes of underlying conditions including, genetic, infectious, metabolic and neoplastic disease processes [5,6.7,8,9,10,11]. The exact pathophysiology resulting in accumulation of calcium at intracerebral sites due to plethora of disease processes remains elusive. Finding intracerebral calcifications incidentally in the scans done for other reasons is also not uncommon [12]. Elderly individuals may have this incidental finding. Usually, these patients do not have any clinical features resulting from the calcification process. On the other hand, individuals who have intracerebral calcifications from systemic diseases such as genetic, infectious, neoplastic diseases do not usually have a benign course. They can have multiple neurologic manifestations including. Neuropsychiatric manifestations, pyramidal manifestations, extrapyramidal manifestations, cerebellar manifestations and disorders of gait and station. On analysis of patients with intracerebral calcifications resulting from a genetic etiology, it has been observed that most of them have autosomal dominant disease [13] which starts manifesting at around middle age. There are some gene loci that have been identified but the exact genomic etiology is still not clearly known.*

*Intracerebral calcifications comprise of two conditions: Fahr's syndrome, in which the calcium deposition is due to disorders of calcium and phosphate metabolism and Fahr's disease which is an idiopathic disorder [14]. Fahr's disease occurs in both familial and sporadic forms. The clinical presentation includes a spectrum of neuropsychiatric features. The aims and objectives of this study included describing clinical profile of patients with intracerebral calcifications and also to identify differences in clinic-radiologic manifestations between patients with Fahr's disease and Fahr's syndrome.*

### *Material and Methods*

*This study was conducted in Department of Neurology, Jawaharlal Nehru Medical College, Datta Meghe Institute of medical Sciences, Sawangi (Meghe) Wardha, Maharashtra India. This is a 1400 bedded tertiary care hospital catering patients from Central part of India. The study was conducted from February 2012 to January 2015. The study was approved by Institutional Ethics Committee of our institute. The study was conducted as per ethical standards according to declaration of Helsinki. Informed written consent was obtained from all subjects prior to enrollment in the study. They were free to leave the study at any point of time. This was a prospective observational study. We screened all patients who presented with presence of intracerebral calcifications on neuroimaging. Because this is a rare disease, and the nature of the study was prospective observational study we did not have any prespecified sample size. We enrolled 22 patients with intracerebral calcifications after obtaining informed consent from them. These patients were evaluated by history taking, clinical examination and laboratory investigations. History was obtained with regards to presenting complains, history of presenting illness, past medical history, social history and family history. The features that were emphasized during history taking were demographic data, presence of seizures, presence of headache, presence of intellectual disability, presence of psychiatric features, presence of Neurosis, presence of psychosis, presence of mood disorders, presence of weakness, sensory loss, presence of extrapyramidal features such as slowness of activities, tremulousness, rigidity, gait disturbances and presence of cerebellar symptoms like incoordination, slurred speech or gait ataxia. The investigations included complete blood counts, liver function tests, kidney function tests, serum calcium level, serum phosphate, serum parathromone, serum vitamin D and thyroid profile. Patients under the age of 18 years were excluded from the study. Those who did not consent were also excluded from the study. Patients with disorders of calcium metabolism were classified as Fahr's syndrome and those without such disorders were classified as Fahr's disease. Various clinical and radiological features were compared between the two groups. Statistical analysis was performed by SPSS version 16 for windows platform. Categorical variables were presented as numbers and percentages. Continuous data were evaluated for normal distribution by Shapiro Wilk test. Continuous variables were expressed as mean (standard deviation) if normally distributed and as median (range) if not normally distributed. Pearson's chi square test was used for comparison of categorical data between different groups. Fisher's exact test was used for small numbers. Continuous data was compared between different groups by two-tailed t-test for independent samples, if the variables were normally distributed. Man- Whitney U test was used to compare continuous data between different groups, for the variables which were not normally distributed.*

### *Results*

*This was a prospective observational study conducted from 2012 to 2015 at a leading tertiary care hospital in Central India. Serial patients who had presented with intracerebral calcifications were evaluated clinically and radiologically. Their clinical data and radiologic data*

*were noted after enrollment and comparison was made between patients with Fahr's syndrome and Fahr's disease as per predefined criteria. During the study period, 500 patients were screened by means of neuroimaging with computed tomography (CT) of the brain and 84 patients were identified. After this, inclusion and exclusion criteria were applied and then study patients were finalized. We identified 22 patients with intracerebral calcifications as study subjects. In terms of gender distribution out of these, 13 (59.1%) patients were females, and nine (40.9%) patients were male. Regarding distribution among different age groups, mean [Standard Deviation (SD)] age of these patients was 40.7 (8.1) years (range 25 – 56 years). When their symptomatology was assessed, the median duration of symptoms was 6 years (range 3 months – 11 years). There was a distinction as well as overlap between the Neurological and psychiatric clinical presentations in these patients with intracerebral calcifications. The clinical manifestations were pure psychiatric in 6 (27.3%); pure neurological in 5 (22.7%) and mixed [psychiatric + neurological] in 11 (50%) patients. We further assessed the various psychiatric manifestations by using a detailed psychiatric analysis and applying criteria according to the Diagnostic and Statistical Manual (DSM) 4 for the psychiatric disorders. Among the 22 study subjects, the frequencies of various psychiatric presentations were as follows: psychosis in 10 (45.5%) patients; neurosis in 9 (40.9%) patients; mood disorders in 10 (45.5%) patients [which included five patients with mania and five patients with depression]. Among the patients with intracerebral calcifications who presented with Neurologic Manifestations, a detailed neurologic history takin and expert clinical examination was done. After this detailed assessment, neurological presentations were as follows: seizures in 8 (36.4%); extrapyramidal features in 10 (45.5%) patients [which included rigidity, bradykinesia, dystonia and tremors; pyramidal features in 7 (31.8%) patients; and cerebellar symptoms in five (22.7%) patients. We also performed detailed systemic examination including the musculoskeletal examination. We found that one patient had skeletal abnormalities in the form of short stature and pectus excavatum. It was also noted that three patients out of the patient population of the 22 patients had clinical signs of hypocalcemia, which notably included carpopedal spasm. The radiologic characteristics were noted in detail by evaluation of Compute d Tomography scans of the brain using 5 mm slice cuts. After this analysis we found that the distribution of intracerebral calcification was as follows: caudate nucleus in 22 (100%) patients; putamen 22 (100%); globus pallidus in 22 (100%); cerebellum in 22 (100%); thalamus in 11 (50%) patients; subcortical in 10 (45.5%); and lobar in three (13.6%) patients [which included various lobes of the cerebrum affecting frontal, parietal and temporal lobes].*

*With regards to the evaluation for etiology of intracerebral calcifications, out of the 22 study patients, we could establish the etiology of calcifications in six (27.2%) patients. These patients were termed as having "Fahr's syndrome". In the remaining 16 patients, it was not possible to identify the exact etiology of the intracerebral calcifications could not be identified. Thus, in our study 6 out of 22 patients had Fahr's Syndrome and 16 out of 22 patients had fah's Disease. The underlying etiology for intracerebral calcium deposition in patients with Fahr's syndrome was identified. These included five patients with hypoparathyroidism [characterized by low serum calcium, low phosphorus and low parathromone level] and one patient with pseudohypoparathyroidism [characterized by low serum calcium, low phosphorous and high parathromone level]. Other investigations including serum proteins, alkaline phosphatase and thyroid profile were normal in all patients. In the remaining 16 (72.7%) patients we could not find the underlying etiology, and these were classified as having "Fahr's disease". Th clinic-radiological differentiation was done between these two groups using statistical analysis. Comparison of clinical and radiological features between the two groups is shown in* ***table 1.***

***Table 1: Comparison of Clinical and Radiologic features between patients with Fahr's syndrome and Fahr's disease***

| ***Parameters*** | ***Fahr's syndrome (n=6)*** | ***Fahr's disease (n=16)*** | ***P value*** |
|---|---|---|---|
| ***Clinical features*** | | | |
| *Mean (SD) age in years* | *38.5 (6.4)* | *41.6 (8.7)* | *0.445 (-5.14 to 11.26)* |
| *Male: Female ratio* | *2:4* | *7:9* | *1.0* |
| *Mean (SD)duration of symptoms in years* | *5.7 (2.6)* | *6 (3.2)* | *0.81 (-2.7 to 3.42)* |
| *Pure psychiatric features* | *2 (33.3%)* | *4 (25%)* | *1.0* |
| *Pure neurological features* | *1 (16.7%)* | *4 (25%)* | *1.0* |
| *Mixed features* | *3 (50%)* | *8 (50%)* | *1.0* |
| *Neurosis* | *4 (66.7%)* | *5 (31.2%)* | *0.178* |
| *psychosis* | *2 (33.5%)* | *8 (50%)* | *0.646* |
| *Mood disorders* | *3 (50%)* | *7 (43.8%)* | *1.0* |

| | | | |
|---|---|---|---|
| *Seizures* | *3 (50%)* | *5 (31.2%)* | *0.624* |
| *Pyramidal features* | *3 (50%)* | *4 (25%)* | *0.334* |
| *Extrapyramidal features* | *4 (66.7%)* | *6 (37.5%)* | *0.348* |
| *Cerebellar* | *2 (33.5%)* | *3 (18.8%)* | *0.585* |
| *s/o hypocalcemia* | *3 (50%)* | *0 (0%)* | ***0.013*** |
| ***Location of Calcification*** | | | |
| *Basal ganglia* | *6 (100%)* | *16 (100%)* | *-* |
| *Cerebellum* | *6 (100%)* | *16 (100%)* | *-* |
| *Thalamus* | *4 (66.7%)* | *7 (43.8%)* | *0.635* |
| *Subcortical* | *2 (33.5%)* | *8 (50%)* | *0.646* |
| *Lobar* | *1 (16.7%)* | *2 (12.5%)* | *1.0* |

***Discussion:-***

*Intracerebral calcification is a commonly encountered radiological anomaly. The etiology of intracerebral calcification is diverse, including CNS infections, malignancies, vascular calcifications, disorders of calcium metabolism and idiopathic intracerebral calcifications. Conventionally, patients with intracerebral calcification due to disorders of calcium metabolism are termed as "Fahr's syndrome" whereas those with idiopathic intracerebral calcification are termed as having "Fahr's disease". The calcification in these conditions involves basal ganglia, thalami and deep cerebellar nuclei. Asymptomatic basal ganglia calcification is noted in 0.9% of general population, most of whom are elderly individuals. However, the exact prevalence of Fahr's disease and Fahr's syndrome are not known.*

*In this study, we evaluated 22 patients with intracerebral calcifications, out of whom 16 patients had Fahr's disease and 6 patients had Fahr's syndrome. Patients had both neurological and psychiatric features at presentation. These included neurosis, psychosis, mood disorders, seizures, pyramidal features, extrapyramidal features and cerebellar symptoms. Geschwind DH et al studied 24 members of a family with Fahr's disease and observed that the main presenting features were dysphagia, focal dystonia, tremor, parkinsonism, and schizophreniform psychosis [13]. On the other hand, König studied 62 patients with sporadic basal ganglia calcifications, and noted that 40% patients had psychiatric symptoms and 50% had neurological features at presentation. The features included intellectual impairment, organic affective syndromes (37% depressive, 20% bipolar and 11% manic cases) [15].*

*The radiological features of Fahr's disease cannot be distinguish from Fahr's syndrome. In our study, the calcifications were noted in basal ganglia, cerebellum, thalamus, lobar and subcortical sites in both group of patients. Furthermore, there were no significant differences in the frequency or distribution of calcification at these sites among the two groups.*

*Etiopathogenesis of Fahr's disease is not known, but it is hypothesized that the intracerebral calcification occurs due to defective iron transport and free radical production in highly metabolic region of brain, leading to local tissue degeneration and metastatic calcification. Although, pallidum is most commonly affected, but calcification has also been found to involve putamen, caudate nucleus, thalamus, corona radiata, and dentate nucleus of cerebellum. Family clustering of FD suggests genetic linkage [16]. Two of our patients were siblings, which also points towards presence of such genetic predisposition. Cognitive impairment in Fahr's disease is fronto-subcortical type and is mostly seen in advanced age. Psychiatric and cognitive impairment could be explained by involvement of frontal-sub cortical network while the involvement of basal ganglia leads to extra pyramidal manifestations. Other clinical features such as behavioral changes and seizures may result from extensive intracerebral calcifications at sites outside basal ganglia. However, there is no specific treatment of Fahr's disease while managing the patients with psychiatric and behavioral manifestation care must be taken while instituting antipsychotic medication because such patients are more prone to develop neuroleptic malignant syndrome.*

*Thus we conclude that idiopathic intracerebral calcification comprises of two entities: "Fahr's syndrome" which includes patients with intracerebral calcification due to disorders of calcium metabolism and "Fahr's disease" which includes patients with idiopathic intracerebral calcification. The common sites of intracerebral calcification in these disorders include basal ganglia, thalamus, cerebellum and cerebrum. The clinical presentations include psychiatric manifestations and neurological features including seizures and extrapyramidal symptoms. There are no significant clinical and radiological differences between patients with Fahr's syndrome and Fahr's disease. These conditions are encountered rarely, but they should be considered in patient's presenting with neuropsychiatric and behavioral abnormality resistant to treatment.*

*There were some limitations of this study. These included a small sample size. This disease being a rare clinical condition, our sample size was small. Furthermore, this was a single center study including patients from a restricted geographical location. In addition, genetic studies including whole genome axon sequencing were not performed due to lack of resources. Hence, we suggest that a multicenter study with a large sample size along with genetic analysis should be performed for a complete understanding of this unusual clinical condition and to differentiate between the two subtypes of patients with intracerebral calcifications.*

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