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Frontotemporal dementia in a Nigerian woman: case report and brief review of the literature.

RO Akinyemi[1,4], MO Owolabi[1], VA Makanjuola[2], AO Ogunseyinde[3] and A Ogunniyi[1].

Departments of Medicine[1], Psychiatry[2] and Radiology[3], University College Hospital, Ibadan and Department of Medicine[4], Federal Medical Centre, Abeokuta, Nigeria

Summary

Frontotemporal lobal degeneration (FTLD) is a clinically heterogeneous group of sporadic and familial neurodegenerative diseases characterized by dementia, alteration in language and/or behaviour, loss of executive skills and sometimes Parkinsonian features resulting from degeneration predominantly affecting the anterior frontal and temporal regions of the brain. Three main clinical subtypes including frontotemporal dementia (FTD), semantic dementia (SD) and progressive non-fluent aphasia (PNFA) have been described depending on the clinical phenomenology, the areas of the brain where the disorder begins and where the most extensive degeneration occurs. We describe a case of frontotemporal dementia in a 58 year old Nigerian woman and also review the current literature. Recent genetic studies have expanded the frontiers of knowledge about FTD while the search for appropriate drug treatments continues.

Keywords: *Frontotemporal, dementia, degeneration, semantic dementia, frontiers.*

Résumé

La dégénération du lobe Frontotemporale (DLFT) est cliniquement un groupe hétérogéne, sporadique et familiale de maladies neurodégénérative caractérisée par la démentie, altération du language et/ou comportement, perte des techniques d'éxecution et souvent les caratéristiques du parkinson résultant de la dégénération prédominant des régions antérieure frontale et temporale du cerveau. Trois sous types cliniques inclut la démentie frontotemporale (DFT), démentie sémantique (DS) et l'aphasie progréssive non-fluente (APNF) sont décrit dépendant de la phénomenologie clinique, des régions du cerveau ou le désordre commence et ou la dégénération plus extensive apparait. Nous décrivons un cas de démentie frontotemporale chez une femme Nigérianne de 58 ans et aussi revisite la littérature courrante. Les études génétiques récentes ont étendues les frontieres des connaissances sur le DFT bien que la recherche des médicaments appropriés continue.

Correspondence: Dr. R.O. Akinyemi, Division of Neurology, Department of Medicine, Federal Medical Centre, PMB 3031, Sapon PO, Abeokuta, Nigeria. Email: rufusakinyemi@yahoo.com

Introduction

Frontotemporal lobal degeneration (FTLD) is a clinically heterogeneous group of sporadic and familial neurodegenerative diseases characterized by dementia, alteration in language and/or behaviour, loss of executive skills and sometimes Parkinsonian features resulting from degeneration predominantly affecting the anterior frontal and temporal regions of the brain [1,2].

Arnold Pick was the first to describe, in 1892, focal syndromes associated with degeneration of the frontal and temporal lobes [3]. Interest was rekindled again about one hundred years later with subsequent development of diagnostic criteria [4,5,6]. This important cause of early-onset dementia is diagnosed mainly during the sixth decade but may affect subjects between the ages of 30 and 75 years [7,8]. Three main clinical subtypes including frontotemporal dementia (FTD), semantic dementia (SD) and progressive non-fluent aphasia (PNFA) have been described depending on the clinical phenomenology, the areas of the brain where the disorder begins and where the most extensive degeneration occurs [8].

In FTD, the degeneration is predominantly bi-frontal (right more than left) and the syndrome is defined by changes in personality, behaviour and executive function while in SD, the nidus of degeneration is predominantly bitemporal with clinical manifestation of disorder of semantic memory for words or people [9]. In PNFA, degeneration occurs predominantly in the left fronto-insular region and the patient predominantly has a non-fluent speech and language problems [10].

However, more recent classification of FTLD is moving from a syndromic approach towards a neuropathologic and genetic-based classification. We are unaware of any previous report of FTD in the

West African sub-region. Herein, we report the clinical and radiological features of FTD in a Nigerian woman followed by a brief review of the current literature.

Case Report

We present a 58 year old female right-handed Nigerian teacher who came to the Neurology Outpatient Clinic of University College Hospital, Ibadan, Nigeria with a two year history of abnormal behaviour and progressive memory impairment which started insidiously. The abnormal behaviour was characterized by inappropriate laughter and crying, reduced conversation which later progressed to incomprehensible sounds and mutism. Her ability to plan and take initiatives was impaired and, over time, she became progressively forgetful and experienced difficulties coping with her teaching job and handling her finances. She required supervision in performing activities of daily living including personal grooming and toileting. She however did not miss her way within the home or wander away in the neighbourhood. There was no history of urinary incontinence, aggression, hallucinations or alteration in level of consciousness. Neither were there seizures, focal limb weakness nor symptoms suggestive of parkinsonism. She had no vascular risk factors and there was no history of alcohol or cigarette use. Although she was involved in a road traffic accident about 18 months before presentation, there was no significant head injury. There was a positive family history of dementing illness in her paternal grandmother.

On examination, she was a middle-aged woman who was conscious and alert, oriented in person but disoriented in time and place. Her registration was poor. Recall, abstraction and calculation were impaired. Short and long term memories were also impaired. Her language functions were impaired; she was economical of speech and repeated verbal expressions after the examiner(echolalia) and sometimes made incomprehensible sounds. However, there were no frontal release signs, cranial nerve, motor, sensory, cerebellar, extrapyramidal or dorsal column deficits. The cardiovascular system was normal with a blood pressure of 140/70mmHg. Other systems were normal.

Computer Tomography scan of the brain revealed significant symmetrical atrophy of the frontal lobes and the anterior part of the temporal lobes with compensatory enlargement of the frontal horns of the lateral ventricle (Figures 1-3). Carotid doppler ultrasonography showed normal carotid arteries. Biochemical and haematological parameters were normal. She attended a single follow up clinic and subsequently relocated to her country home about 300 kilometers away from Ibadan. She had a follow up visit in the country home undertaken by her doctors on one occasion about eighteen months after her initial presentation at the clinic. She had become totally mute and unable to recognize any of her children. She was inattentive, aspontaneous, emotionally flat and neglected her personal care. She was incontinent of urine. She ate excessively, made repetitive movements with her limbs and paced up and down in the living room of her apartment. She touched or picked objects within reach or sight. She was dependent on family members for all activities of daily living.

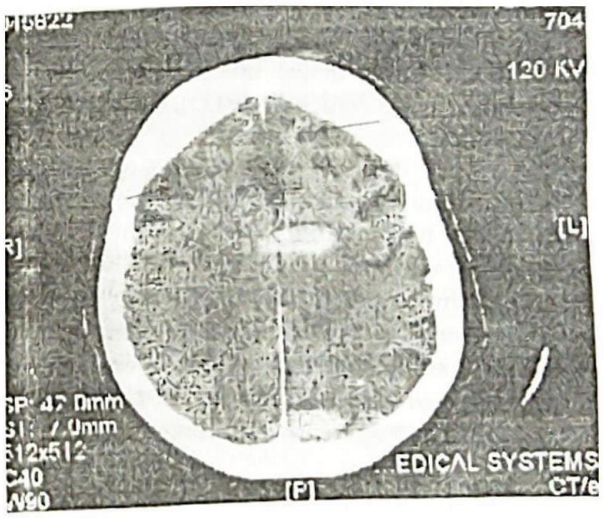

Fig. 1: Cranial tomography scan of the subject showing severe atrophy of the frontal lobes (arrows)

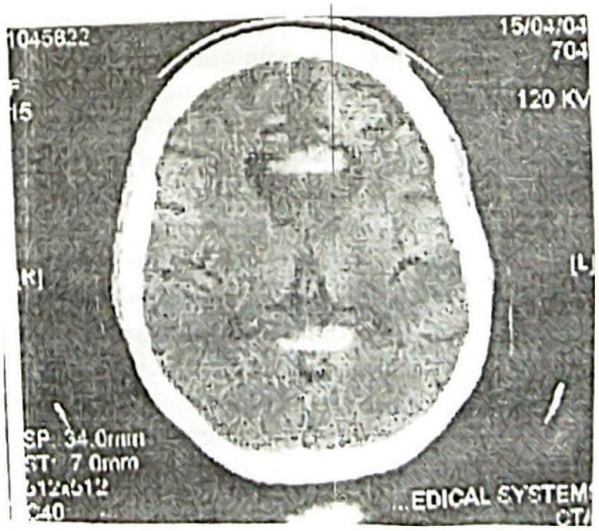

Fig. 2: Cranial tomography scan of the subject showing frontal atrophy and compensatory dilatation of the anterior horns of the lateral ventricle (arrows)

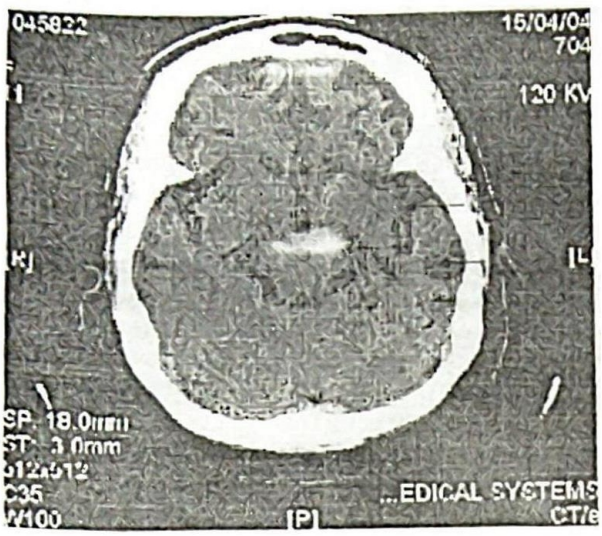

Fig. 3: Cranial tomography scan showing atrophy of frontal and parts of temporal lobes (arrows)

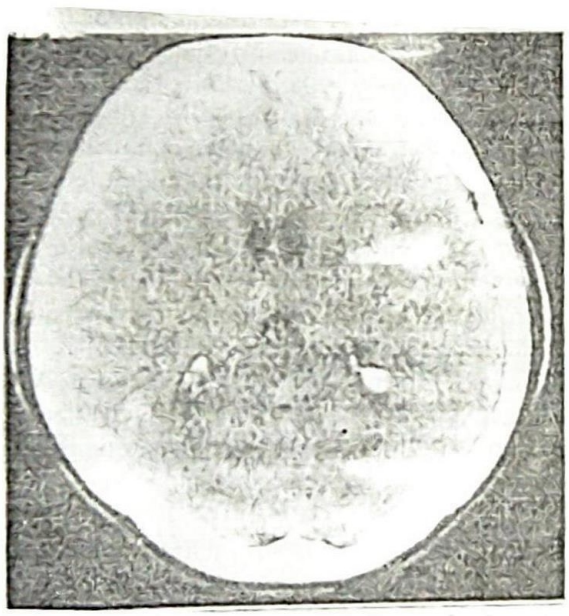

Fig. 4: Normal CT brain scan for comparison

Discussion

In 1998, certain criteria for the clinical diagnosis of fronto-temporal dementia (FTD) were formulated in the Lund/Manchester consensus statement [6]. The patient in this case report met those criteria for the clinical diagnosis of FTD. The core criteria include progressive decline in social conduct, personal regulation, insight and emotional reactivity, all of which were present in the patient. Other behavioural manifestations of frontal lobe syndrome itemized in the criteria include decline in personal hygiene and grooming, distractibility, impersistence, hyperorality and utilization behaviour. Speech and language abnormalities including aspontaneity, economy of speech, echolalia, perseveration, stereotypy and mutism are supportive features in the diagnostic criteria that were also present in our patient. Our patient had no significant vascular risk factors and her brain CT demonstrated no significant infarcts that may suggest previous vascular events.

The onset of FTD is insidious, occurring most often in the presenile age range of 45 to 65 years into which our patient falls. There is a 2:1 male preponderance and a positive family history in up to 25-40% of subjects [11]. Data on prevalence and incidence are scarce. In a UK study, the prevalence was estimated at 15 cases per 100,000 persons in the 45 –to- 64- year-old-range [12] while in another study from Netherlands, prevalence was 3.6 cases per 100,000 persons at ages 50-59 years, 9.4 per 100,000 at ages 60-69 years, and 3.8 per 100,000 at ages 70-79 years [13]. Apart from novel mutations recently described in a South African family with FTD, there are no other reports from Africa [14].

The occurrence of genetic mutations in the FTLD syndromes vary across the different subtypes, FTD being most strongly familial in 40% of cases while 10% show an autosomal dominant pattern of inheritance [15,16]. FTLD was first linked to chromosome 17 in 1994 [17]. Mutations in the gene encoding the macrotubule-associated protein tau (MAPT) have been identified in families with FTLD with tau pathology and till date, over 40 different mutations in the tau gene have been reported [18,19,20]. Other tauopathies with described tau mutations include corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP) [21,22].

More recently, certain families were described with genetic linkage to the tau region but absent tau mutations. They were shown to have mutations in the progranulin gene also on chromosome 17 [23,24]. Progranulin is a growth factor which deficiency results in neurodegeneration. In FTD patients with progranulin mutations, TAR DNA-binding protein 43 (TDP-43) has been identified as a major disease protein in ubiquitin-positive neuronal inclusions [25]. Other uncommon genetic mutations causing FTD are Valosin-containing Protein (VCP) gene mutations [26] and mutations on chromosome 3 [14].

Neuropathologically, FTD demonstrates predilection for specific brain regions. The anterior frontal, insular and temporal regions are severely affected while some changes are also seen in the

hippocampus, amygdala, substantia nigra, putamen, caudate and globus pallidus [27]. However, the posterior parietal, posterior temporal and occipital cortices are usually spared. The presence of hippocampal sclerosis in association with FTD explains why many patients with FTD also show memory problems as seen in the current case report. The pathological processes of FTD begin in certain selectively susceptible neurons that develop late in ontogeny and phylogeny (Von Economo neurons) which are located in the anterior cingulate, anterior insular and orbitofrontal regions of the frontal cortex [28]. Current subtyping is done based on the presence or absence of neuronal and glial inclusions which may be tau positive, ubiquitin-TDP-43 –positive or tau negative [25]. Approximately 50% of FTD patients are tau positive while the other 50% are TDP-43 positive. Most patients with Progressive Non-fluent Aphasia (PNFA) are tau positive while most patients with Semantic Dementia (SD) are TDP-43 positive [29,30].

Neurotransmitter systems with demonstrable deficiencies in FTD include those of serotonin and dopamine, while the acetylcholine system appears relatively intact [31]. Autopsy, functional imaging and CSF studies have shown deficits in serotoninergic transmission, the deficits being more postsynaptic than presynaptic [32]. There are also strong dopaminergic projections to the areas of the frontal cortex which degenerate in FTD [33]. While the FTDP-17 (frontotemporal dementia and parkinsonism) variant has strong clinical evidence of basal ganglia dopamine dysregulation, there are also PET and SPECT studies that have demonstrated evidence of decreased presynaptic dopamine transporter in the putamen and caudate of patients with FTD [34].

While there is currently no specific treatment that can offer symptomatic improvement or delayed progression in FTD, current strategies employ medications to treat behavioural symptoms based on neurotransmitter replacement/augmentation as done for other neurodegenerative diseases such as Alzheimer's disease(AD). Based on the serotoninergic deficits in FTD, selective serotonin reuptake inhibitors have been used with some improvement in behaviour but not in cognition [35]. Atypical antipsychotics may become necessary in highly agitated and aggressive patients. There is really no place for anticholinesterase compounds while further studies are ongoing to develop better treatments.

Conclusion

We have reported a case of frontotemporal dementia in a middle-aged Nigerian woman and also reviewed the current literature. Recent genetic studies have expanded the frontiers of knowledge about FTD while the search for appropriate drug treatments continues.

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