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Intelligence Impairment, Personality Features and Psychopathology Disturbances in a Family Affected with CADASIL

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Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a small-vessel disease of the brain that is characterized by headache, recurring lacunar strokes, mood changes and progressive cognitive deterioration. The disease is transmitted with an autosomal dominant pattern and usually starts during midadulthood (at 30–50 years of age). Cognitive deficits in patients with CADASIL develop slowly. The dementia causes frontal-like symptoms and it typically develops after a history of recurrent stroke. We describe three patients from one Spanish family affected by this disease. All three cases underwent comprehensive clinical and neuropsychological examination, and were monitored for seven years. The results obtained in this study describe a) a significant loss of the intelligence quotient (IQ) and noticeable damage to abstract ability (g factor), b) mood and psychopathological disturbances (major depression and dysthymia), and c) a personality with neurotic features.
Keywords: CADASIL, intelligence, personality, psychopathology, vascular dementia.

La arteriopatía cerebral autosómica dominante con infartos subcorticales y leucoencefalopatía (CADASIL) se caracteriza por una alteración de las arterias cerebrales de pequeño y mediano calibre. La presentación clínica incluye migraña, infartos cerebrales recurrentes, cambios del humor y deterioro cognitivo. La enfermedad se transmite siguiendo un patrón autosómico dominante e inicia su desarrollo entre los 30-50 años de edad. El deterioro cognitivo evoluciona lentamente hasta un cuadro similar al de la demencia frontal, y con frecuencia se desarrolla tras un periodo previo de episodios isquémicos recurrentes. Este trabajo describe a tres pacientes de una familia española afectada por la enfermedad. Se les siguió durante un período de siete años. Con el fin de estudiar la evolución del cuadro, se efectuaron diversas pruebas clínicas y neuropsicológicas. Los resultados obtenidos muestran a) una disminución significativa del cociente de inteligencia (CI) y un notorio deterioro del factor de inteligencia general (factor g), b) alteraciones psicopatológicas (depresión mayor y distimia), y c) un perfil de personalidad de rasgos neuróticos.
Palabras clave: CADASIL, inteligencia, personalidad, psicopatología, demencia vascular.

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Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is the cause of a monogenetic small-vessel disease of the brain. Mutations of the Notch3 gene on chromosome 19 have been identified as the genetic defect underlying this condition (Joutel et al., 1996). Radiological tests reveal deep cerebral infarcts and wide diffuse leukoencephalopathy with characteristic involvement in the temporal poles (Auer et al. 2001). The condition is described as an arteriopathy with extravascular granular osmiophylic deposits adjacent to the basal membrane of the soft muscle cell, degeneration of the small muscle cell and median layer, and obliteration of the lumen (Ruchoux & Maurage, 1997). The clinical spectrum of CADASIL is broad, but its most significant symptoms are migraine with aura, recurrent ischemic episodes, cognitive deterioration and dementia, and psychopathological disorders (Chabriat et al., 1995). Migraine with aura and ischemic episodes—in the form of transient ischemic attacks (TIA) or stroke—appear in relatively early stages of the disease and have been described and studied in greater detail. However, information on the other two symptoms—cognitive damage and psychological disorders—is scant. In general, the available studies merely report the clinical observation of symptoms, without accurately measuring them or analyzing their development pattern. Therefore, this study aims to analyze the progressive impairment associated with CADASIL in three areas: intelligence, personality, and psychopathological alterations.

Method

Participants

Three patients with CADASIL belonging to the same family and attending a specialist neurological center as outpatients were invited to participate in the study (patients A, B and C in Table 1). A healthy relative was used as control participant (called D in Table 1). After informed consent had been obtained, all participants underwent detailed clinical, neuropsychological, and neuroimaging studies, and a thorough examination to exclude treatable causes of dementia. In all patients, skin biopsy revealed spotted formations in the extravascular regions of the wall of the arterioles and venules in the dermis and subcutaneous tissue. In all of them, the diagnosis of CADASIL was confirmed also by detection of the mutation c.463 T>A (Cys155Ser) in exon 4 of the Notch3 gene.

Patient A. A 58 year old man with a confirmed diagnosis of CADASIL. The patient was a diabetic (diabetes mellitus) with no clinical history of hypertension, substance use (except cigarettes—he smoked 30 per day until about 10 years ago), head trauma, or psychopathological alterations. He had had frequent migraines since he was 20 years old, a symptom which he shared with his mother and grandmother, both dead when this study was carried out. A brother of the patient died from dementia, though we have no details of his clinical history. Our patient was admitted at age 49 due to an ischemic episode with a clinical picture of motor dysphasia and right hemiparesis. An MRI revealed ischemic infarction in the left semioval center and multiple bilateral periventricular white matter (hyperintense) lesions in frontal, temporal and occipital horns, basal ganglia and external capsule. At age 51 the patient suffered a new episode with left visual field loss (left homonymous inferior quadrantanopia) accompanied by confusional state, increasing difficulties for holding a conversation, and racing thoughts. A right temporo-occipital subcortical ischemic infarct was observed. At age 56 he suffered from ischemic cardiopathy with uncomplicated myocardial infarction and was in treatment with β-blockers and platelet antiaggregants.

Patient B. A 33 year old woman (patient A's daughter) with a confirmed diagnosis of CADASIL who had normal arterial pressure values and has been a smoker since age 17 (20 cigarettes per day). She had no history of substance use, head trauma or psychological condition. Like her father, she had experienced frequent attacks of migraine with aura since she was 20 years of age. At age 23 she was admitted due to basilar artery migraine with a clinical picture of headache and paresthesia in both hands and perioral territory, with unstable gait and a bilateral visual field defect. These episodes reoccurred approximately once or twice per year. She was readmitted at age 30 after a cesarean delivery with right hemiparesis, language alterations, and a visual field defect in the right hemifield. The process resolved itself in 10 days with no apparent sequelae. An MRI study showed subcortical confluent lesions at the anterior poles of the temporal lobes and in parasagittal regions of the frontal lobes, as well as multiple isolated lesions in periventricular white matter.

Patient C. A 30 year old man (patient A's son and patient B's brother) with normal arterial pressure values who was a habitual smoker (about 20 cigarettes per day) and an occasional user of marijuana, with no clinical history of interest. He carried the same mutation as his relatives, though he had no migraines or cerebral ischemic episodes. Nevertheless, an MRI revealed nonconfluent hyperintense lesions that were significantly numerous for his age, with involvement of the temporal uncus and subcortical white matter.

Control D. A 32 year old man, who was the son and brother of the other patients, with no relevant clinical history. He was an ex-smoker and occasional narcotics user (marijuana). The presence of CADASIL was ruled out by the immunostaining skin biopsy and molecular genetic testing. No functional alterations were observed in a neuropsychological examination.

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Table 1
Individual patient demographic and clinical data.

	Patients (A, B, C) and control participant (D)			
	A	B	C	D
Age (years)	58	33	30	32
Gender	male	female	male	male
Kinship	father	daughter	son	son
Education (years)	10	15	15	15
Profession	bank teller	administrative	unskilled worker	unskilled worker
Stroke-like episodes	yes	yes	no	no
Onset	49 years	22 years		
Migraine	yes	yes	no	no
Epileptic seizures	yes	no	no	no
Hypertension	no	no	no	no
Diabetes	yes	no	no	no
Vascular risk factors	smoker	smoker	smoker	smoker
Skin biopsy	+	+	+	-
MRI with leukoaraiosis	yes	yes	yes	no
Degree of WM lesions[1]	3	2	1	0

Note. [1] Scale for age-related white matter (WM) changes (Wahlund et al., 2001): 0 (No lesions), 1 (Focal lesions), 2 (Beginning confluence of lesions), 3 (Diffuse involvement of the entire region, with or without involvement of U fibers).

Instruments

All the participants were assessed twice, with a seven-year interval. On both occasions they were asked to complete a test battery including:

Intelligence test

Wechsler Adult Intelligence Scale (WAIS). The first evaluation used a Spanish adaptation of the WAIS (Weschler, 1977), whereas the second used the adaptation of the third edition (Weschler, 1997). At the second assessment four additional factors were calculated: verbal comprehension (VC), working memory (WM), perceptual organization (PO), and processing speed (PS).

Raven Standard Progressive Matrices (SPM) (Raven, Court, & Raven, 1996). As a contrast to the Wechsler test, which is more saturated in crystallized intelligence (Colom, Abad, García, & Juan-Espinosa, 2002), the Raven test was included in the evaluation protocol as a measure of fluid intelligence.

Personality test

Minnesota Multiphasic Personality Inventory (MMPI) (Hathaway & McKinley, 1988).

CEP personality questionnaire (Pinillos, 1982). This questionnaire is made up of three personality scales: emotional stability (control), extroversion and paranoia, and two auxiliary scales: sincerity and amount of doubts.

Clinical examination

A clinical psychologist (F.J.D-S.) evaluated the presence of mental or personality alterations in each of the patients and in the non-affected relative. In all cases, the diagnostic examination was accompanied by application of the Spanish version of the clinical interview structured for axes I and II of DSM-IV (First, Spitzer, Gibbon, & Williams, 1999; First, Gibbon, Spitzer, & Williams, 1999).

Results

Intelligence tests

– *WAIS IQs*. Table 2 shows the results obtained by the 4 probands in the two evaluations carried out during the follow-up. In general, the members of this family showed a high intellectual capacity in the first evaluation, obtaining "bright average" (patients B and C) or "very high" (control D) on the WAIS. The only exception was patient A, who had an IQ within the normal range.

In the second evaluation, all the patients suffered a significant loss of IQ, more severe than would be expected for their age. Thus, patient A's IQ fell to a "normal low" range, while those of patients B and C fell to average values, within the range of normal. In contrast, control D remained in the "very high" range. All the famiy members, including the healthy control, showed striking discrepancies between VIQ and PIQ scores. In all cases, the VIQ was much higher than the PIQ. This discrepancy was not a casual fact, but remained constant throughout follow-up. Analysis of the cognitive function indices of the WAIS (Figure 1) reveals a similar pattern in all the patients, contrasting clearly with what was observed in the healthy control. Figure 1 shows

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Table 2
Evolution of Wechsler's Intelligence Quotients (Verbal-VIQ, Performance-PIQ, Full scale-FSIQ) and General Intelligence Factor (SPM-IQ).

		Patients (A, B, C) and control participant (D)			
		A	B	C	D
VIQ	1st Asses.	110	121	120	134
	2nd Asses.	101	103	110	132
Loss (%)		8.2	14.9	8.3	1.5
PIQ	1st Asses.	78	108	106	118
	2nd Asses.	76	96	93	115
Loss (%)		2.6	11.1	12.2	2.5
FSIQ	1st Asses.	96	117	115	130
	2nd Asses.	88	99	102	125
Loss (%)		8.3	15.4	11.3	3.8
SPM-IQ	1st Asses.	48	114	115	114
	2nd Asses.	36	103	105	109
Loss (%)		25	9.7	8.7	4.4

that all the probands scored high in VC, but only the carriers of the mutation scored low in PO, PS and WM. The last two of these indices showed an inverse relationship with the level of white matter deterioration ($r_s = -1$; $p < .01$, for PS; $r_s = -.95$; $p = .05$, for WM), evaluated through the *Scale for age-related white matter changes* (Wahlund et al., 2001).

– *g factor*. The general intelligence factor (*g*), showed a clear progressive impairment depending on the duration of the disease (Table 2). Thus, the loss in this area was more noticeable in patient A and, in decreasing order, in patients B and C. This index correlated inversely with the level of white-matter deterioration ($r_s = -1$; $p < .01$) and positively with PS ($r_s = 1$; $p < .01$).

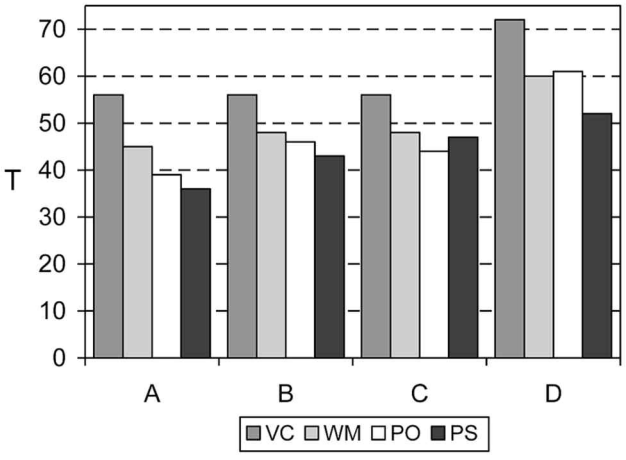

Figure 1. T scores of patients A, B, C and control D in Verbal Comprehension (VC), Working Memory (WM), Perceptual Organization (PO) and Processing Speed (PS).

Personality features

The relevance of the personality features (Table 3) was determined following a double criterion: test score (T score ≥ 60 in the MMPI, centile score ≥ 80 in CEP) and variability in the feature throughout follow-up. Fulfillment of one or both criteria by any of the patients decided the choice of one scale or another. The data obtained reveal a personality profile common to all the patients, which is more defined and intense the longer the condition lasts. The distinctive characteristics of this profile are increasing emotional instability (neuroticism) associated with an excessive concern for health and well being (hypochondria), a dysthymic pessimistic mood (depression), which in A and B was accompanied by irritability, suspicion and apprehension (paranoidism), and an attitude of withdrawal and avoidance of social situations (introversion) in the patient whose condition lasted longest (A). Nevertheless, the last two features, suspicion and introversion, also appeared in the healthy control.

Psychopathological disturbances

Psychological examinations revealed specific symptoms of a mood disorder in patients A, B, and C. These symptoms fall into four categories: affective (depressed mood and feelings of worthlessness), behavioral (social withdrawal and slowness), cognitive (difficulty with concentration or making decisions), and somatic symptoms (insomnia or hypersomnia and neurasthenic symptoms). In accordance with the DSM-IV criteria (APA, 2000), the symptoms of patients A and B were compatible with a dysthymic disorder (F34.1). Furthermore, patient A had

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Table 3
Outcome of personality profile. T scores for personality traits affected in the first and second evaluations.

	Patients (A, B, C) and control participant (D)			
	A	B	C	D
	1st – 2nd	1st – 2nd	1st – 2nd	1st – 2nd
Depression	81 – 86	58 – 69	46 – 60	55 – 50
Hypochondria	68 – 71	65 – 62	61 – 60	42 – 37
Neuroticism	72 – 78	58 – 68	72 – 61	43 – 36
Introversion	66 – 82	43 – 48	36 – 40	61 – 70
Paranoia (CEP)	57 – 57	58 – 60	47 – 44	57 – 58

major depression (F33.2) superimposed on the dysthymia (double depression).

Discussion

This longitudinal study was carried out to evaluate the process of impairment associated with the clinical course of CADASIL in three areas: intellectual abilities, personality profile, and psychopathological alterations. To this end, we carried out a follow-up of a family with ideal characteristics for this type of investigation: carriers of the Notch3 mutation and a healthy blood relative who acted as the control and served as a reference. Similarly, patient availability at different stages of the disease (Verin et al., 1995) made possible a cross-sectional study of the effects of this condition on the areas mentioned above.

Intellectual abilities

– *WAIS IQs*. In the family studied, the evolution of CADASIL was accompanied by a general loss of aptitudes affecting both VIQ and PIQ. This process of impairment presents some peculiar characteristics that are worthy of comment. On the one hand, the loss of IQ points does not seem to be stable during the course of the disease; thus, the most severe losses appear in the earliest phases (patients B and C) and are attenuated in the more advanced stages (patient A). On the other hand, the impairment of the intelligence indices (VIQ, PIQ and FSIQ) can already be found in the early stages of the disease, regardless of whether clinical symptoms (migraine or ischemic episodes) are present (patient B) or not (patient C). This observation is in line with the results to date in cross-sectional studies, which point to an early onset of cognitive alterations (Amberla et al., 2004; Peters, Opherk, Danek, Ballard, Herzog, & Dichgans, 2005), and contrasts with those of other studies that suggest a later onset of these alterations (Lesnik et al., 2003; Trojano, Ragno, Manca, & Caruso, 1998). The disparity of the results may be due to the excessively short follow-up intervals (2 years in the study by Trojano et al., 1998), which would be insufficient when trying to detect possible cognitive deficits if these develop insidiously or appear abruptly after a somewhat longer period. Nevertheless, these results may also reflect subtypes or variations in the course of the disease, which would lead to early cognitive impairment in some cases and to later cognitive impairment in others.

One psychometric trait that is common to the members of the family studied is that they all present a marked VIQ-PIQ discrepancy, with significantly higher scores on the WAIS verbal scale. This imbalance between the two types of IQ does not seem to be associated with a specific stage of the disease, since it was detected in all the carriers of the mutation in the two evaluations performed during follow-up. Moreover, the fact that it is also present in the healthy control seems to indicate that this is more a case of a typical characteristic of this family group. There is also the possibility that subtle alterations in the Notch components can lead to specific cognitive functioning. In this regard, an animal study (Costa, Honjo, & Silva, 2003) shows how this type of alteration generates specific learning and spatial memory deficits, factors that are included in the measurement of PIQ. Similarly, some authors point to the existence of genes that would modulate the response of brain tissue to the cerebrovascular condition and that, consequently, would also determine the cognitive impairment profile associated with it (Leblanc, Meschia, Stuss, & Hachinski, 2006).

– *g Factor*. In our patients, the progress of CADASIL was also associated with a progressive loss of the capacity for abstract and analogical reasoning, the g factor. This general intelligence index has been considered a psychometric representation of the functionality of the frontal lobes. Its impairment is related to the alteration of the executive functions mediated by the prefrontal areas of the brain and its frontal and subcortical reciprocal connection pathways (Duncan, 1995; Roca et al., 2010). Similarly, subcortical or periventricular white matter lesions, such as those observed in our patients, have been associated with a gradual deterioration of general cognitive ability (Deary, Leaper, Murray, Staff, & Whaley, 2003) and, particularly in the case of CADASIL, with the dysfunction and impairment of the executive processes (O'Sullivan, Barrick,

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Morris, Clark, & Markus, 2005). In our study, white matter alteration is related to a reduction in processing speed (PS index). This slowing-down in the management of information could be affecting both, the executive functions and cognitive processes, such as working memory (WM index), keys to general intellectual functioning. The slowdown in PS means that information is not processed with the necessary rapidity, thus hindering and eventually collapsing the development of cognitive processes. Furthermore, as information tends to decay quickly in working memory (WM), slow processing could limit considerably the capacity to access this information and to retain in the memory data that are relevant for the development of different cognitive functions (Fry & Hale, 2000). Previous studies have found a similar profile of impairment, and highlight as early characteristics of the disorder the slowdown in processing speed and the subsequent impairment of executive functions (Amberla et al., 2004; Peters et al., 2005). In summary, the data in our study suggest that CADASIL produces an impairment that affects both crystallized intelligence (reflected in the IQs of the WAIS) and fluid intelligence (reflected in the g factor of the Raven test). A detriment in the latter type of intellective ability could be related to the alteration of a multioperational system (executive functions) that affects both the control and planning of behavior and the direction and organization of cognitive processes.

Personality features

In the family examined in this study, the development of CADASIL is associated with changes in the personality profile. Specifically, patients develop neurotic traits, which, at the functional level, reflect greater difficulty for managing and confronting situations of stress, conflict, or decision-making, and which are related to a high level of anxiety and, in general, a poorer level of mental health (Deary & Matthews, 1993). Furthermore, a more marked emotional variability is observed in this type of patient, with a tendency toward dysthymia, dysphoric feelings and hypochondria. These modifications in the personality profile become apparent in early stages of the disease, though in our patients they did not start simultaneously—the neurotic and hypochondriac traits were presented first and the dysthymic symptoms appeared insidiously as the disease progressed.

The available data do not enable us to offer a sound explanation for the origin of these changes in patient personality structure. The neurological alterations associated with the condition, together with the emotional reactivity or indeed regardless of this reactivity, could be responsible for the changes observed in the personality profile. Specifically, the lesions affecting the prefrontal and subcortical circuits, typical of vascular dementia and particularly of CADASIL, could be the cause of these modifications (Auer et al., 2001; van den Boom et al., 2003).

Psychopathological disturbances

Cerebrovascular disease frequently progresses with neuropsychiatric complications that can make recovery and social adaptation difficult, thus limiting the patient's quality of life. Depressive symptoms are one of the most common psychopathological manifestations in this area, and are an important risk factor for severe stroke (Jonas & Mussolino, 2000). These mood alterations are also common in patients with CADASIL; in fact, the three members affected in our study presented depressive symptoms whose severity and clinical picture varied according to the developmental stage of the disease and to the severity of the lesions in the white matter. We still do not know the mechanisms responsible for the appearance of this affective syndrome. However, psychological and biological factors may explain the occurrence of these mood disorders: several studies indicate that a neurotic personality profile increases vulnerability to the emergence of post-stroke depression (Aben et al., 2002), and some data correlate the severity of subcortical white matter lesions with the onset and persistence of symptoms of depression (Steffens, Krishnan, Crump, & Burke, 2002). Once again, the structural and functional alterations of the frontal-subcortical connections could play an important role in the pathogenesis of this type of condition by involving neuronal networks that regulate our affective state and our emotional reactions in response to the demands of our environment (Davidson, Pizagalli, Nitschke, & Putnam, 2002).

In summary, the results of this study suggest that the natural history of CADASIL may include the following: (a) A stepwise deterioration of basal IQ, with marked losses in verbal and motor-spatial skills and pronounced damage to abstract ability; (b) A personality profile whose distinctive features are increasing emotional instability (neuroticism), and hypochondriac and depressive traits; (c) Specific symptoms of a mood disorder: Dysthymia or major depression.

Our study has several limitations. First, the basic data have been taken from a small sample of first-degree family members, which restricts the possibilities of generalization of the results. Nevertheless, CADASIL presents marked genotypic and phenotypic variations that lead to a heterogeneous and specific course of the condition in each family. This makes it difficult to establish evolutionary schedules or stages that are common to all the patients, and supports the study of phenotypic manifestations of the condition in specific family groups, rather than in patient groups whose genotype is varied.

Second, the conclusions drawn about the course of impairment in the areas studied are based partly on the cross-sectional evaluation of the family members. Therefore, these inferences must be treated with caution until they can be considered alongside those from a future longitudinal follow-up of these patients.

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