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Neuropsychologic phenotypes in familial hemiplegic migraine

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Abstract Familial hemiplegic migraine (FHM) is a rare autosomal dominant-type migraine with aura. Attacks are characterised by hemiparesis in addition to other aura and migraine symptoms. Few studies have examined the influence of FHM on cognitive functions. This study was aimed to investigate neuropsychological functions in 3 adolescent siblings suffering from FHM assessed six months after the last attack. No relevant deficits were found on a battery of multisectorial tests exploring cognitive functions. Sporadic FHM attack therefore seems not to affect cognition in these patients, at least far from the crises.

Key words Familial hemiplegic migraine • Neuropsychologic phenotypes • Cognitive functions

Introduction

Familial hemiplegic migraine (FHM) is a rare autosomal dominant-type migraine with aura which is inherited by dominant trait, even though there are reports of sporadic occurrence [1–4]. A single familial hemiplegic migraine locus has been previously mapped to chromosome 19p13.1 [3–13]. Studies in different FHM families showed that additional causative genes must reside in other regions of the genome, including the long arm of chromosome 1 [5, 8, 9, 12, 14, 15].

Crises, which occur especially during development, generally show an annual frequency. Hemiplegia, which is associated in hemianesthesia, can involve the hemisome as a whole, or it can be localised in the upper part, involving in particular the face [3, 5, 14–16]. During the attack, a state of confusion is often present and it can be compared to a psychotic state (visual or acoustic hallucinations) [5, 16, 17]. In patients in whom the dominant hemisphere is involved, aphasia is also present [5, 14, 18].

Marchioni et al. [19] demonstrated potential cognitive dysfunction in 3 of 5 family members, who complained about repeated attacks of hemiplegic migraine, migraine with aura of different types, or migraine without aura. At least two months after their latest attacks, they showed dyscalculia, attention disturbances, and impaired long-term verbal memory during neuropsychologic assessment. In another study, the severity of cognitive impairment was correlated with severity of migraine history [18], however the cognitive impairment has never been investigated near to an FHM attack. The purpose of this study was to determine, through a battery of multisectorial tests, if cognitive impairment, not related to the occurrence of the attack, was evident in patients with FHM. Thus, I studied the neuropsychological phenotypes of three adolescents with FHM from the same family.

Subjects and methods

The 3 adolescents studied are from a large family in which the mother and 6 of 8 children are affected by FHM. The affected children are 4 males aged 33, 30, 15 and 13 years, and 2 females aged 30 and 10 years. Convulsions with fever were reported by the

mother and 4 of the 6 affected children (the males aged 33, 15 and 13 years and the 10-year-old girl). The convulsive symptoms accompanied by fever occurred within the first year of life (mean age, 8 months). For the present study, the 15- and 13-year-old boys and the 10-year-old girl were examined with a neuropsychological test battery. Clinical characteristics of the disease were obtained from anamnesis and examination of medical records.

Neuropsychological assessment

The neuropsychologic assessment was carried out 6 months after the latest FHM episode. The neuropsychological tests included:

- *Wechsler intelligence scale for children-revised* (WISC-R) is used to evaluate the intellectual abilities of children aged 6–16 years. It is composed of 12 subtests exploring specific abilities in the verbal sphere (information, similarities, arithmetic, vocabulary, comprehension, digit span) and performance sphere (picture completion, picture arrangement, block design, object assembly, coding, mazes). Verbal tests evaluate linguistics, comprehension, and visual-perceptive and spatial angles. Three different forms of intelligence quotient (IQ) are given: verbal IQ, performance IQ, and total IQ.
- *Raven's progressive matrices test*, organized into 36 items, measures the ability of a subject to formulate comparisons, to argue from analogies, to see some figures as a spatial whole, connected among themselves, and to analyse the components of the figures.
- *Zazzo's deux barrages test* requires subjects to distinguish and mark as quickly as possible specific symbols or signs mixed with others. The test measures the attention capacity by evaluating the drop in efficiency and the level of integration and coordination of complex attitude.
- *Benton's visual retention form D test* evaluates visual-spatial, perceptive and immediate memories and visual motor functions. It consists in 10 cases, each containing one or more geometric figures: each case is shown to the subjects for 10 seconds; then, after 15 seconds, they are asked to reproduce the figure.
- *Frostig's developmental test of visual perception* (DTVP) explores visual perceptive development in children with learning difficulties by analysing specific areas in the development of perception which are relatively independent from each other. The test is composed of 5 subtests: visual-motor coordination, figure background, constancy of shape, position in space, and spatial relationship.
- *Rey's complex figure test* uses a complex figure, deprived of semantic references, composed of a series of straight lines, angles, triangles, parallel right lines, all superimposed. The subject must first copy and, after an interval of time, reproduce the images by heart. The test evaluates the perceptive framing, the application, visual-motor capacities, and the capacity of short-term retention (spontaneous visual memory, without voluntary memory).

Results

Three adolescent siblings with familial hemiplegic migraine (FHM) were studied (Table 1). All subjects had normal findings at computed tomography and magnetic resonance imaging. Electroencephalography (EEG) previously performed during attacks showed theta abnormalities over the contralateral hemisphere in all patients. Interictal EEG showed theta abnormalities with left predominance in cases 1 and 2.

Table 1 Clinical characteristics of 3 adolescent siblings affected with familial hemiplegic migraine (FHM)

	Case 1	Case 2	Case 3
Age, years	15	13	10
Gender	M	M	F
Age at first observation, years	6	5	6
Hemiplegic attacks, n	10	6	4
Migraine with aura	Yes	Yes	Yes
Hemiparesis	Yes	Yes	Yes
Affected side	right of left	right of left	right of left
Duration of paresis, hours	2	2	1
Progressive impairment of consciousness	Yes	Yes	No
Aphasia	No	Yes	Yes
Coma	No	No	No

Table 2 Neuropsychology test results in 3 adolescent siblings with FHM

	Case 1	Case 2	Case 3
WISC-R			
Total IQ	92	94	102
Performance IQ	91	95	92
Verbal IQ	94	97	103
Raven's progressive matrices			
Centile	>75	>75	>75
Zazzo's *deux barrages*			
Speed and efficiency			
V1	123.1	122.6	121.9
V2	57.6	56.8	58.5
R1	142.1	143.6	144.1
R2	131.7	130.7	129.9
Error and quotients			
1N1	0.17	0.19	0.20
1N2	0.27	0.29	0.27
QV	0.92	0.91	0.93
QR	1.06	1.07	1.05
Benton's visual retention form D			
Correct position	4.7	4.8	4.9
Omission	2.5	2.7	2.3
Distortion	3.3	3.4	3.1
Perseverance	0.8	0.1	0.5
Rotation	0.9	0.8	0.5
Wrong placing	1.5	1.7	1.4
Wrong dimension	0.07	0.08	0.05
Left	3.6	3.7	3.1
Right	4.8	3.9	3.2
Total errors	9.3	9.1	8.7
Frostig's visual perception			
Visual-motor coordination	81.0	82.0	81.1
Figure of background	70.5	71.1	70.1
Constancy of conformation	68.9	70.2	70.8
Position in space	71.2	71.9	79.7
Spatial relationship	79.4	80.3	80.6
Rey's complex figure			
Copy score	35	36	36
Copy time	8 min 50 s	9 min 1 s	7 min 56 s
Type of copy	IV	IV	IV
Reproduction score	33	32	34
Type of reproduction	IV	IV	IV

WISC-R, Wechsler intelligence scale for children-revised; *IQ*, intelligence quotient

Neuropsychological testing revealed that none of the 3 subjects had significant cognitive deficit (Table 2). According to WISC-R test, all had an average IQ score (mean values: total IQ, 96; performance IQ, 94; verbal IQ, 98). The screening with the other tests did not demonstrate a relevant impairment of the functions examined, with the exception of Frostig's visual perception test. All 3 patients showed difficulties in these tests, especially

when distinguishing a figure from the background and when examining the constancy of the figure, namely identifying a geometric figure of different dimension and position.

On Rey's figure test, the 3 patients were able to find parts of the perceptive field and reproduce them to represent the proportions among all four figures, to discriminate among intersecting elements and the difficulty to reproduce, and showed good capacity of attention to drawing details. The corporeal scheme indicated the patient in relation to the others and to the principal and secondary images. The graphic description was complete in the fundamental sides and in some of secondary sides.

In case 3, a mild and non-significant impairment in the long-term verbal memory was detected as was a minor attention deficit. This patient also had slight difficulties in the immediate auditive memory, and in recent memory.

All 3 patients had low scores on Zazzo's *deux barrages* test, confirming a slight deficit of attention and concentration. The level of organization, concerning visual-motor, visual-perceptive and visual-spatial capacities was also lower than that expected for the patient's chronological ages.

Discussion

Neuropsychological impairment in migraineurs has been described since 1986 [20, 26]. Deficits in attention, early visual processing [27, 28], memory [20–25], and psychomotor abilities [20, 24, 29] were reported in patients with migraine with aura assessed in the interictal period [30]. Cognitive impairment involving memory and psychomotor abilities was also shown in subjects with migraine without aura [20, 30].

A recent study carried out by Mulder et al. [31] showed that migraineurs without aura responded as quickly as controls, while migraineurs with aura were slower during all tasks specifically requiring selective attention. These effects were not aggravated by a preceding migraine attack, and not related to medication used or to attack duration.

The pathophysiological mechanism underlying cognitive deficits in migraine, particularly with aura, is a matter of debate [32]. It was hypothesized that persistent abnormalities in cerebral blood flow causing neuronal disturbances and a complex neurotransmitter disorder may account for reduced short- and long-term memories in migraine patients [22, 33]. However, other studies found neither detrimental cognitive effects in migraine patients nor differences between migraineurs with and without aura, when they were assessed interictally [34–36].

Cognitive impairment was found in family members affected by FHM and also suffering from attacks of migraine with and without aura [19]. The cognitive impairment was more severe when the migraine history was more pronounced. To our knowledge, no other reports on cognitive function in FHM are available.

The present study was therefore aimed to assess, through a battery of multisectorial tests, some neuropsychological functions and the presence of sectorial defects in 3 FHM patients evaluated in the interictal period. These patients did not have any brain anomaly evident on neuroimaging.

No relevant neuropsychological deficits were found in the 3 cases studied, with the exception of the 10-year-old girl in which a mild impairment of attention, concentration and recent memory emerged.

We can explain, at least in part, the discrepancy between the previous report by Marchioni et al. [19] and our results with regards to the differences in the patients assessed. FHM patients examined in the study of Marchioni et al. [19] were also affected by migraine with and without aura. In particular, although the frequency of FHM in these patients was of a few attacks per year, they complained of more frequent episodes of migraine aura of different types and also of migraine without aura. This is not the case in the 3 patients included in our study, who suffered only from hemiplegic migraine attacks with an annual frequency. We hypothesize that migraine per se in the patients assessed in Marchioni et al.'s study [19] contributed to their cognitive impairments independently from the FHM attacks, and this could be related to the severity of the migraine crises which was more pronounced in patients experiencing higher frequency of attacks and in those with a long history of migraine. The authors of the previous research [19] alternatively hypothesized that their patients may have had a syndromic association such as autosomal dominant HM and cerebellar ataxia described by Fitzsimons and Wolfenden [37], associated with cognitive disturbances. There was no evidence of cerebrellar symptoms in our 3 FHM patients and we excluded this hypothesis for our cases.

Further studies should be carried out with a larger number of patients with FHM to clarify the discrepancies in the findings obtained until now. Data should be carefully examined in light of the clinical phenotype, including the occurrence of other types of migraine with and without aura, the frequency of attacks and timing from the last attack. The cognitive impairment, if any, should be interpreted taking into consideration also haemodynamic changes measured by PET and SPECT and results from new neuroimaging techniques, such as magnetic resonance spectroscopy.

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