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Early detection of Huntington's disease. Blink reflex and levodopa load in presymptomatic and incipient subjects

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SUMMARY The R2 response on the blink reflex was found to be abnormal in seven out of 17 Huntington's disease descendants. Such abnormalities were present in four untreated subjects and in three further subjects after administration of a single oral dose of levodopa-carbidopa. An increase in latency and differential latency (four cases), or in a single one of these parameters (three cases) were the abnormalities found, resembling findings in four incipient cases detected during routine family surveys. Continuous administration of levodopa-carbidopa over a 10–20 day period did not induce new characteristics in the blink reflex, nor increase those detected previously, and no case developed chorea. We suggest that the analysis of the blink reflex after a single oral levodopa-carbidopa dosage could provide an objective and quantifiable method for the detection of individuals at risk for Huntington's disease.

Huntington's disease (HD) is due to a dominant gene of high penetrancy, yet the presence or absence of this abnormal gene can not usually be ascertained until obvious physical signs appear in the affected individual. Numerous predictive tests have been developed, but at present none is definitely reliable.[1 2] Oral levodopa increases chorea in affected patients through altered striatal response to dopamine.[3] There are no data to show at which age this abnormal susceptibility develops but Klawans *et al*[4 5] reported that one-third of presymptomatic HD descendants developed transient facial or limb dyskinesias or both after receiving oral levodopa and assumed that they would later develop the disease. Mainly because of uncertainty as to how to interpret these results, these investigators now rarely, if ever, use this test.[2]

Various parameters of the late response (R2) of the electrically evoked blink reflex are abnormal in HD[6-8] and previous data suggested that once changes can be demonstrated even in early incipient cases. Levodopa is known to modify this reflex; its pattern in Parkinson's disease is reversed by treatment.[9 10] It appeared that in presymptomatic subjects at risk of HD submitted to a levodopa predictive test, the simultaneous examination of the blink reflex possibly would provide a more sensitive and quantifiable method of detection than the simple visual search for choreic movements.

In this study, 17 HD descendants were observed for the presence of dyskinesias and the blink reflex pattern before and after a levodopa load, and were compared to four incipient cases and normal controls studied under similar conditions.

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Methods

Ethical guidelines

The use of a predictive test for an incurable disease such as HD is a matter of controversy. While some have instigated investigations requiring cooperative effort,[4 5] others feel them unjustified mainly because the lack of an effective treatment and the impression that at-risk subjects prefer to live in the hope of being unaffected.[11] In practice, however, the right of an individual to be fully informed with all the information available, and subsequently to make a personal choice cannot be overlooked. The ethical

guidelines in the design of the present investigation were based on two crucial points. First, a full yet compassionate discussion of the information about the consequences and uncertainties inherent in the procedure was given, in such a way to allow a personal decision based upon solid grounds. Then, if the results of the test were positive, the individual received continuous supportive counselling to sustain his emotional needs and demands for further information and medical help. All families involved in this study were contacted by the Spanish Group of the Committee to Combat Huntington's Disease.

Once the diagnosis was established in the propositus and the family tree outlined, at-risk subjects were individually informed of the genetic consequences of the disease, the lack of any effective treatment at present and about the research project. The tentative nature of the results for predicting the risk for the future development of the condition was anticipated as well as the need of future retesting in the years to come to validate the results. It was announced that the effect of levodopa should be on the electrophysiological aspects of the study, but that there was a risk of inducing transitory involuntary movements. Subjects freely expressed their personal decision only after a second attendance; in case 10, a 9 year old girl, the decision was assumed by her guardian.

Groups involved

Three groups of subjects were studied (table 1). Normal volunteers (group A) comprised 20 individuals (nine men and 11 women) with a mean age of 30·5 years (range, 12 to 51 years). HD offspring group (group B) consisted of 17 subjects in whom one parent had had a definite diagnosis of the disease. There were eight men and nine women whose mean age was 28·8 years (range, nine to 58 years). Four subjects (two men and two women) formed the incipient HD group (group C) having a mean age of 40·5 years (range, 23 to 50 years). At this time they all had minimal, yet undisputable choreic movements, usually only in the face and hands; because of this, their relatives were already suspicious of the diagnosis in two cases, but they were unaware in the others.

Levodopa load tests

A single oral dose of combination of carbidopa-levodopa in one to ten ratio (Sinemet-25/250) was given as an acute test. The chronic test consisted of a stable dose of 1 g of levodopa per day (plus 100 mg of carbidopa) for at least four days, this having being achieved through gradual increments over a 10 to 20 day period (table 1). Seven subjects of group A received a mean dose of levodopa of 390 mg (range 350 to 500 mg) in the acute test and a mean total dose of 10 g in the chronic test, ranging from 7·25 to 14·35 g. In group B, 15 individuals underwent the acute test (mean dose of 430 mg, ranging from 200 to 500 mg) and 11 had the chronic test (mean total dose of 9·2 g, ranging from 5·25 to 13 g). In group C, three cases were submitted to the acute test, receiving a mean dose of 415 mg (range, 375 to 500 mg).

Blink reflex

Percutaneous alternating electric shocks were delivered to the supraorbital nerve at its emergence on both sides. Responses were detected by means of coaxial needle electrodes inserted at the outer third of both lower eyelids. A Medelec MS5 electromyography device was used for recording. Quadrangular wave stimuli were of fixed duration (0·5 ms), but the intensity required to produce a well-defined R1 response varied for each subject (25-100 volts). Five responses were obtained, interval between the electrical shocks being greater than 15 s. The parameters of the late (R2) response were evaluated as described in a previous paper.[6] In short, the latency was defined as the mean value of both maximal and minimal values of the ipsilateral responses. Differential latency was defined as the difference in latency between the R2 response obtained ipsilateral and contralateral to the stimulated side; its mean value was similarly obtained. The habituation index was expressed as the frequency of stimulation at which the last ipsilateral R2 response, after a series of 10 consecutive stimuli, had a value (amplitude per duration) of less than 20 per cent of that in the first (it was measured independently on each side). Basal trends were obtained from every subject, and the second was reported forty to ninety minutes after levodopa ingestion in the acute test, care being taken to keep the electrodes in place. Finally, a third examination was carried out while the subject was taking levodopa chronically. The presence of abnormal involuntary

Table 1 *Mean age of normal controls, Huntington's disease unaffected offspring and incipient cases, and mean total L-dopa dosage (given with carbidopa) in load tests*

	Normal controls			*Huntington's disease Descendants at risk*			*Incipient Huntington's disease*		
	N	*Mean age (yr)*	*L-dopa total dose mean (range)*	*N*	*Mean age (yr)*	*L-dopa total dose mean (range)*	*N*	*Mean age (yr)*	*L-dopa total dose mean (range)*
Basal	20	30	—	17	28·8	—	4	40·5	—
Acute test (mg)	7	31·7	390 (350-500)	15	26·5	430 (200-500)	3	37·6	415 (375-500)
Chronic test (g)	6	30	10 (7·25-14·3)	11	25·8	9·2 (5·25-13)	—	—	—

N = number of cases

movements, as well as the ability to forcefully maintain eyelid occlusion and tongue protrusion was assessed before every electrophysiological recording.

Statistical evaluation
Results were statistically analysed by student's *t*-test.

Results

Levodopa-induced involuntary movements No normal control or HD descendant developed clinically evident involuntary movements while taking levodopa acutely or chronically. On close inspection case 2 in group B had minimal facial grimacing at the end of the chronic test and case 14 (group B) showed some inability to maintain the eyelids tightly closed, but we felt that this probably was due to anxiety. In contrast, two out of the three incipient patients given a single oral dose of levodopa developed a marked enhancement of chorea, although no changes were seen in the third patient.

Blink reflex Values from different R2 response parameters in all three groups are expressed in table 2. No differences from the normal controls were found after acute or chronic levodopa ingestion. Mean basal valu' in HD descendants did not differ from control values ($p>0.05$), and they were similar also after either form of levodopa load, both when compared to their own basal values or to those from normal subjects.

When individually analysed (table 3), four out of 17 HD descendants showed an abnormal blink reflex pattern in basal conditions (cases 1, 5, 7 and 15). After the acute levodopa test, an increase in the severity of the previous abnormalities occurred in case 1, and two further cases (cases 4 and 16) became abnormal. After the chronic levodopa test, no increase in the severity of the previously recorded abnormalities was found and no new abnormalities appeared in the HD descendants. A further subject (case 10), which was the only one not examined under basal conditions because of her young age, appeared abnormal after the acute levodopa load. Both latency and differential latency were the abnormal parameters recorded from four cases, while the other three had abnormalities in only one of these parameters (figure). Furthermore, each of these seven cases had a habituation index value below the mean in control subjects (0·71). None of the three parameters evaluated differed from normal controls, before or after levodopa in the other 10 descendants. The two individuals (cases 2 and 14, table 3) in which the presence of levodopa-induced dyskinesias was questioned clinically, experienced no changes in their blink reflex patterns. The mean age of HD descendants having an abnormal blink reflex (28·4 years) was similar to those having normal values (29·3 years). A nine year old girl, who was the youngest subject examined from group B, had also the more severe degree of abnormal blink reflex. The onset of HD in her mother was at 23 years and several other affected members from her family, including case 3 of group C, also had an unusually early onset of the disease.

Table 2 *Basal blink reflex and after acute or chronic administration of levodopa (carbidopa) (mean ±1 SD)*

	Latency	*Differential latency*	*Habituation index*	*P*
Normal Controls				
Basal	31±2·85	2·46±1·92	0·71±0·25	—
Acute test	31·5±3·1	3·03±2·43	0·58±0·2	>0·05
Chronic test	29·5±3·1	2·29±1·95	0·8±0·18	>0·05
HD offspring				
Basal	31·8±2·9	2·06±3·16	0·67±0·31	>0·05
Acute test	32·05±3·2	2·45±4·79	0·66±0·4	>0·05
Chronic test	30·7±3·3	2·13±3·57	0·62±0·29	>0·05
Incipient HD				
Basal	38·1±2·3*	4·18±3·9†*	0·48±0·03‡	<0·001* >0·05†
Acute test	39·8±4·3*	5·75±6·6†*	0·47±0·07‡	<0·05‡

P, when compared with the basal values of normal control subjects.
HD—Huntington's disease.

Mean latency and habituation index values from these four cases of incipient HD (group C) differed from normal controls ($p<0.001$ and $p<0.05$, respectively), both before and after the acute levodopa provocative test (table 2). Basal individual latency values also were greater than the maximum normal value (36·7 ms) from the control group (table 4; figure). A further shift towards abnormality was obtained after the acute administration of levodopa and, in addition, the differential latency also became abnormal in two cases, in parallel with a levodopa-induced deterioration of the choreic movements. The patient in whom there was no appreciable increase of the choreic movements on levodopa (case 2, table 4) also was the only one in which the blink reflex pattern remained unmodified.

Discussion

The incipient HD group consisted of four fully employed individuals, unaware of their illness which was detected during routine family surveys. Nevertheless, it was obvious to the experienced neurologist that they had mild yet characteristic choreic movements. This group had a R2 response of their blink reflex modified in a

Table 3 *Basal blink reflex in Huntington's disease offspring and after L-dopa/carbidopa load tests*†

Case/age (yr)	*Basal*			*Acute test*			*Chronic test*		
	L	*DL*	*HI*	*L*	*DL*	*HI*	*L*	*DL*	*HI*
1 AMH 26	30	9·5*	0·5	28	21*	0·5	31·5	13*	0·5
	37·5*	−2·5*	0·7	38*	−6*	0·5	33	−2*	0·6
2 LCN 17	30	6	0·7	28·5	2	0·5	28	3	0·5
	30	1·5	0·5	30	3	0·5	28	1·5	0·5
3 ECN 30	30	2	0·5	29	3·5	0·45	30	1	0·5
	31	1·5	0·5	30	3	0·45	30	1	0·5
4 JLCN 27	26·5	5	0·5	26·5	3	0·5	26·5	−1·5*	0·5
	27	–	0·5	28	−2·5*	0·5	27	−2*	0·5
5 CCN 19	33	−1·5*	0·5	31	4	0·5	29·5	3·5*	0·25
	29	−0·5	0·5	31·5	−2*	0·5	31	−2*	0·25
6 PSP 52	33·5	3·5	0·5	–	–	–	36	5	0·5
	31	4	1	–	–	–	36	5·5	0·5
7 JSP 45	33	1	0·5	32·5	1	0·45	–	–	–
	37*	0·5	0·5	35·5	0	0·45	–	–	–
8 AMS 30	30	2·5	0·8	28·5	−1	1	–	–	–
	30	1·5	1	29·5	4	2	–	–	–
9 MCM 19	33·5	1·5	0·5	32·5	4·5	0·5	–	–	–
	31·5	4	0·5	33	0	0·5	–	–	–
10 DCM 9	–	–	–	40*	9·5*	–	–	–	–
	–	–	–	41*	2	–	–	–	–
11 MSS 26	35·5	4·5	0·5	30	3·5	0·5	32·5	1	0·5
	32·5	−0·5	0·5	35	0	0·5	32·5	2	0·5
12 JAJP 21	30	1	1·5	32·5	3	1·5	31	1	1·5
	32	3	1·2	32	2	1·2	32	2·5	1·2
13 AIJP 22	30	2·5	1	30·5	1	1	27	1	1
	29	0	1	29·5	1	1	28·5	−0·5	1
14 PJP 18	32·5	2	1	32	−1	0·7	28·5	2	0·7
	31	0	1	32·5	0·5	0·5	27	5·5	0·7
15 VSS 26	35·5	10*	0·5	34	7*	0·45	32·5	7·5*	0·4
	40·5*	−6*	0·5	34	−1·5*	0·45	39·5*	−1	0·5
16 FJP 45	30·5	4·5	0·6	32	9*	0·5	–	–	–
	33·5	2·5	0·5	36·7*	2	0·5	–	–	–
17 LMG 58	30·5	0·5	0·5	–	–	–	–	–	–
	33	0·5	0·5	–	–	–	–	–	–

†Values from right (upper) and left (lower) sides in each case L = Latency (in ms); DL = Differential latency (in ms); HI = Habituation index.
* = Abnormal values, beyond normal control mean basal values ± 2 SD.
Negative values of DL means that R2 response contralateral to the stimulated side appears earlier than the ipsilateral one.

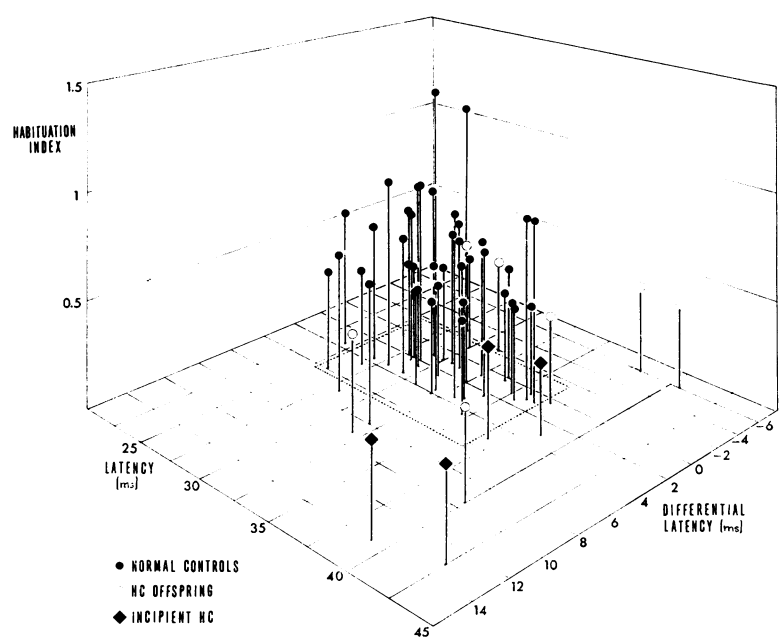

Figure *Mean values ± 2 SD of latency and differential latency of the R2 response of the blink reflex on both sides from a sample of 20 healthy subjects are represented within the dotted line (rectangle). Seven out of 17 Huntington's disease descendants and the four incipient cases are placed outside. No case with abnormal blink reflex findings had a habituation index value over 0·5. Values represented were those which displayed the greatest deviation from normality, whether or not under basal conditions or after a levodopa-carbidopa administration.*

Table 4 *Blink reflex in incipient Huntington's disease cases*

Case/age (yr)	Basal			Acute L-dopa/carbidopa test		
	Latency	*Differential latency*	*Habituation index*	*Latency*	*Differential latency*	*Habituation index*
1 AGM 49	37*	3	0·5	–	–	–
	38·5*	3	0·4	–	–	–
2 JLGF 40	34	4	–	36	4	–
	37*	5	0·5	35	4	0·5
3 TMM 23	37·5*	5·5	0·5	39*	14*	0·5
	39*	1	0·5	40·5*	3	0·5
4 MER 50	40*	12·5*	0·5	42·5*	13*	0·5
	42·5*	–0·5	0·5	46*	–3·5*	0·35

Values from right (upper) and left (lower) sides in each case. Latency and differential latency in ms.
* = Abnormal values, beyond normal control mean basal values ± 2 SD

similar way to those in patients with advanced disease.[6] The failure of Ferguson *et al*[8] to demonstrate blink reflex abnormalities in their young patients could be explained on the basis that latencies and differential latencies, which were the most severe abnormalities usually found in our series, were not examined. Similar to overt HD[3] all but one of our incipient cases deteriorated in the severity of chorea when a single oral levodopa dose was administered. Parallel to the enhancement of chorea, there was a further shift toward abnormality of the previously altered R2 patterns.

Seven out 17 individuals from the HD descendants group (41%) displayed significant abnormalities in their blink reflex. The impaired parameters were latency and differential latency, similar to incipient and advanced HD patients. The abnormalities occurred for both parameters in 23·5% of the cases, while in the other 17·6% it was for one parameter only. The abnormalities were already present under basal conditions in four cases while in the other three they were shown after the acute administration of levodopa (case 10, because of her early age, was examined only under the later condition). In normal subjects, acute or chronic administration of HD descendant caused no change in the blink reflex. As no developed levodopa-induced involuntary movements, the present results suggest that both the blink reflex abnormalities and their modifications by levodopa occur well before the appearance of choreic movements, either spontaneous or drug-induced. The effects of acute administration of levodopa in HD descendants were unmodified after two to three weeks of levodopa intake, so it appears that the chronic test did not provide any practical advantage over the acute test. None of our 11 HD descendants developed overt or definite choreic movements while under levodopa given over a 10 to 20 days period. These results do not agree with those of Klawans *et al*,[4 5] who reported that about one-third of their HD descendants developed mild chorea, mainly in the facial area, while on chronic levodopa. The dose schedules were similar in both studies and cannot account for this discrepancy. There are no other references in the literature regarding the effect of levodopa as a provocative test to induce chorea in presymptomatic subjects. Cawein and Turney[12] and Husquinet *et al*[13] induced a clearcut increase in the severity of chorea in individuals who had already mild abnormal involuntary movements before any treatment with levodopa (as in our incipient group C).

We plan to retest and publish the results after a five year period of observation of the HD descendants. Either an increase in the electrophysiological abnormalities already detected in still clinically unaffected subjects, or the emergence of the disease during that time may occur, but it may take much longer to decide whether the test does give reliable predictive information. We would encourage other groups to undertake the present investigation and to check its reproductibility in individuals at risk demanding a predictive test. Not only does it provide objective quantifiable abnormalities, but it avoids the unwanted situation of prematurely facing the subject with the image of his eventual illness by inducing chorea.

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