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GESTION PHARMACOLOGIQUE DE LA MH : UNE REVUE CRITIQUE BASÉE SUR L'EVIDENCE.

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Introduction: On peut identifier trois groupes de traitements médicaux dans la HD s'attaquant au déclin cognitif, aux problèmes de comportement et au dysfonctionnement moteur. Malgré la croissance du nombre des rapports publiés sur les interventions pharmacologiques, il n'a pas encore été publié de recensement des études des traitements, basées sur des preuves intrinsèques.

Méthode: Les recherches systématiques des textes ont été faites avec Medline (1965-août 2005), la base de données centrale de la Bibliothèque Cochrane, et les listes référencées publiées dans des articles de revue ou autres rapports cliniques.

Dans cet article, les études de niveau I correspondent à des essais contrôlés randomisés (RCT), le niveau II, aux études cliniques contrôlées non randomisées, le niveau III, aux études ouvertes (le malade et le médecin connaissent le médicament utilisé). On prend en compte, pour chaque composé, des critères (et mesures) d'efficacité, de sécurité et de tolérance.

Résultats: Nous avons identifié 218 publications sur des interventions pharmacologiques pour HD depuis 1965. Elles concernent 20 niveau I, 55 niveau II, 54 niveau III et 89 rapports de cas. Tous ces documents ont été inventoriés et analysés.

La chorée était le premier point final dans tous les essais symptomatiques des niveaux I et II. Il ressort des études des preuves positives pour le traitement de la chorée par haloperidol ou fluphenazine, mais moins par olanzapine. Dans cette analyse, nous avons considéré ces trois médicaments comme pouvant être utiles dans le traitement de la chorée. D'autres substances pour le traitement de la chorée. nécessitent des études approfondies (par exemple amantadine, riluzole et tétrabénazine).

Il y a une faible évidence pour le traitement des autres problèmes: des médicaments peuvent être utiles comme L-dopa et pramipexole pour la rigidité; amitryptiline et mirtazapine pour la dépression, rispéridone pour la psychose; olanzapine, haloperidol et buspirone pour les symptômes comportementaux dans HD.

L'étude de trois substances: : coenzyme Q10, minocycline, et des acides gras insaturés doit être approfondie pour envisager une neuroprotection.

Conclusion: La gestion pharmacologique de la HD semble aujourd'hui faiblement convaincante.

Les analyses des 20 études de niveau I ne font apparaître aucune recommandation de traitements de pertinence clinique.
La grande qualité des RCT est une garantie pour les progrès des traitements cliniques.

Pharmacological Management of Huntington's Disease: An Evidence-Based Review

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Abstract: Introduction: Despite the increasing body of published reports on pharmacological interventions in Huntington's disease (HD), an evidence based review (EBR) of treatment studies has not yet been published.

Method: Systematic literature searches were done using Medline (1965 – August 2005), the central database in the Cochrane Library (1969 – August 2005), and reference lists published in review articles and other clinical reports. Randomized controlled trials (RCTs) were classified as level-I-studies in this paper. Level-II evidence was assigned to non-randomized, controlled clinical studies. Level-III-studies comprised open label trials excluding case reports. Measures of efficacy as well as safety and tolerability were considered for each compound.

Results: We identified 218 publications on pharmacological interventions in HD since 1965. Among them were 20 level-I, 55 level-II, 54 level-III trials, and 89 case reports. All these papers are listed and analyzed. Chorea was the primary end point in all level-I and level-II symptomatic intervention trials. There is some evidence for treating chorea with haloperidol or fluphenazine, and less evidence for olanzapine. These three drugs have been considered "possibly useful" for the treatment of chorea in this analysis. Other substances (e.g. amantadine, riluzole, and tetrabenazine) are considered "investigational" for chorea. There is very low evidence for the treatment of other problems: "possibly useful" drugs are L-dopa and pramipexole for rigidity; amitriptyline and mirtazapine for depression; risperidone for psychosis; and olanzapine, haloperidol, and buspirone for behavioral symptoms in HD. Three substances are considered "investigational" for possible neuroprotection: coenzyme Q10, minocycline, and unsaturated fatty acids.

Conclusion: There is poor evidence in management of HD today. The analysis of the twenty level-I studies fails to result in any treatment recommendation of clinical relevance. High-quality RCT are highly warranted to advance HD treatment in clinical practice.

Key Words: Huntington's disease, therapy, chorea, neuroleptics, neuroprotection.

INTRODUCTION

Three groups of treatment problems can be identified in clinical practice in Huntington's disease (HD): cognitive decline, behavioral problems and motor impairment. However, established therapeutic interventions in HD are rare today. They are not equally accessible and their real clinical value has not always been established through high quality, randomized, controlled clinical trials. Despite the increasing body of published reports on therapeutic interventions in HD

[1], these have never been critically reviewed. We therefore conducted a systematic evidence-based review (EBR) of pharmacological therapy in patients with HD. To this end, we followed the recent EBR of the management of Parkinson's disease (PD) [2]. In the present EBR, we excluded non-pharmacological strategies, which will be reviewed separately.

METHOD

Literature searches were done using electronic databases including Medline (1965 – August 2005), the central data-

base in the Cochrane Library (1969 – August 2005), and systematic searches of reference lists published in review articles and other clinical reports. We identified 218 publications with original data on pharmacotherapy in HD (ten of the on side-effects). All these studies are systematically analyzed in this review and appear in one of the tables. Where appropriate, also papers published between 1950 and

1964 are cited without being systematically analyzed, and without inclusion into the tables. The publications are grouped based on a hierarchical organization of evidence. Analogous to the PD-EBR, randomized controlled trials

(RCTs) represent level-I-studies in this review if additional criteria are fulfilled: (a) minimum of 2 weeks treatment period on active drug, (b) minimum of 10 HD patients on active drug completing the study, (c) full paper citation. Controlled trials that did not fulfill these criteria were assigned to level-II. In addition, non-randomized or observational controlled trials were classified as level-II. Level-III was assigned to uncontrolled case series, i.e. open label trials and retrospective reports. Finally, case reports were considered the lowest level of evidence. Papers were accepted regardless of their language and rating scales provided latter were operationally defined. In general, a genetic diagnosis of HD was not required; reports were accepted based on the clinical diagnosis. Twenty of the trials fulfilled the criteria for level-

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I, 55 were rated as level-II, and 54 as level-III (Tables 1-3). In addition, there were 79 case reports dealing with pharmacological management of HD (Table 4). Finally, ten studies reported side effects, but no efficacy data (Table 5).

The level-I-studies were additionally rated with respect to the study quality. The study quality score was derived from a list of key methodological topics, according to a published checklist, relevant for determining the methodological soundness of the trial [2]. The papers were studied by their results, selection criteria, measurement, statistical analysis, and utility of the outcome. A percentage score was calculated for each study and was used as an indicator of the overall quality of the study. All ratings were done by both authors independently, the differences in scores were reviewed and a consensus reached among them. A study with a study quality of 75% and more was considered as a high quality, or level Ia trial; below this percentage, the study was considered level Ib. Safety profiles and tolerability of the substance considered are described using a narrative, non-systematic approach for each trial of interest. The clinical information used to make an overall safety evaluation included adverse reactions reported in the trial, adverse reactions reported in the product information documents, and literature reports based on non-systematically searched papers. Assessment of efficacy and safety for each therapeutic intervention were made followed by specific implications for use in clinical research.

Efficacy was standardized in five categories: Efficacious – Likely efficacious – Unlikely efficacious – Non efficacious – and Insufficient evidence [2]. A substance was considered efficacious when evidence showed that it has a positive effect on the measured outcomes, supported by data from at least one high-quality (score \geq 75%, i.e. level Ia) RCT without conflicting level-I-data (irrespective of the quality). A substance was considered likely efficacious when evidence suggests, but is not sufficient to show, that it has a positive effect on studied outcomes. These findings have to be supported by data from any RCT (irrespective the quality) without conflicting level-I-data. A substance was considered unlikely efficacious when evidence suggests, that it does not have a positive effect on studied outcomes. These findings have to be supported by data from any RCT (irrespective of the quality) without conflicting Level-I-data. A substance was considered not efficacious when evidence shows that it does not have any positive effect on studied outcomes, supported by data from at least one high-quality (score \geq 75%) RCT without conflicting Level-I-data (irrespective of the quality). And, finally, a substance was considered insufficient evidence when there is not enough evidence either for or against efficacy in treatment of HD, counting all the circumstances not covered by the previous statements. Safety was divided into four categories: acceptable risk without specialized monitoring – acceptable risk with specialized monitoring – unacceptable risk – insufficient evidence to make conclusions on the safety of the intervention.

The specific implications for use in clinical research were divided in five categories: Clinically useful (For a given situation, evidence available is sufficient to conclude that the intervention provides clinical benefit) – Possibly useful (For a given situation, evidence available suggests, but insuffi-

cient to conclude that the intervention provides clinical benefit) – Investigational (Available evidence is insufficient to support the use of the intervention in clinical practice, but further study is warranted) – Not useful (For a given situation, evidence available is sufficient to conclude that the intervention provides no clinical benefit) – and Efficacy unlikely (Evidence suggests that the intervention provides no clinical benefit).

This review is divided into the following sections: (a) treatment of chorea. (b) treatment of other neurological features, (c) treatment of psychiatric symptoms, and (d) neuro-protective treatment strategies .

A. Treatment of Chorea

A.1. Conventional Dopamine-Blocking Medications

Conventional antipsychotic drugs are still used to treat chorea in clinical practice. They are widely accepted to have significant antichoreic effects, although complications like aggravated parkinsonism, impaired balance, difficulties in swallowing, apathy, and dysphoria limit their utility [3]. Furthermore, all three level-I trials of conventional antipsychotic drugs had disappointing or contradicting outcomes [4-6]. *Haloperidol*, still a widely established antipsychotic drug, was never studied in a level-I HD trial. There is evidence from three level II [7-9] and three level III studies [10-12] that it may be effective in ameliorating HD-related chorea. In detail, haloperidol (2-80 mg/d; dosage was increased until chorea was suppressed) was effective in a single-blinded (videotapes presented to blinded observer) trial of 13 patients of unclear study duration [8], but failed to reduce chorea in six patients on 15 mg/d in a double-blind, crossover comparison to lithium [13]. However, a further single-blind, cross-over study [7] of 11 patients showed an equal efficacy of haloperidol compared to tetrabenazine with less severe adverse effects in the haloperidol group, although tardive dyskinesia complicated haloperidol therapy in three of 11 patients. Barr *et al.* [10] found low-dose haloperidol (less than 10 mg per day) to be effective to reduce chorea in an open pilot study with little added clinical benefit on doses above 10 mg per day. Two other Level-III trials [11, 12] and three case reports [14-16] found comparable positive results in favor of haloperidol. Also older reports suggest its effectiveness [17-19].

Fluphenazine, another conventional antipsychotic, was effective in reducing chorea in a small level II trial [20], confirmed by level-III data [21] and a case report [22]. The substance was widely used in the 60ies [22]; all reports originate from this period. Trials of *tiapride* in HD produced contradictory results. A level-Ib study [5] reported antichoreatic effects (confirmed by a level II study [23]), however, these results were contradicted by another level-Ib paper [6] and two level-III [11, 24] studies. In contrast, on *pimozide* there are four positive small level-III studies [11, 25-27] and a negative case report [28]. *Sulpiride* reduced chorea scores in a level Ib trial [4], although functional improvement was not seen; an additional case report showed good efficacy [29]. A series of positive papers of the 60ies and 70ies suggest *thiopropazate* [30-34], although out of use in the last 20 years. Finally, trials with *trifluoperidol* [35], *thiopropazine*

Table 1. Level I Studies 1965 - 2005

	Active drug	Versus	First author, year	HD diagnosis	Effect	n =	Study design	Study duration	HD score	Study quality	Evidence Level
Antidopaminergics											
1	haloperidol	placebo	Quinn, 1984	clinic	poor effect	11	crossover	4 weeks	CSS	74	lb
2	haloperidol	placebo	Deroover, 1984	history	positiv	23	crossover	3 weeks	self	61	lb
3	haloperidol	placebo	Roos, 1982	history	no effect	22	crossover	2 weeks	video, self	63	lb
4	clozapine	placebo	van Vugt, 1997	CAG	poor effect	26	crossover	4 weeks	AIMS UHDRS	72	lb
NMDA-antagonists											
5	amantadine	placebo	O'Suilleabhain, 2003	CAG	no effect	24	crossover	2 weeks	video, self	89	la
6	amantadine	placebo	Verhagen, 2002	CAG	positiv	24	crossover	2 weeks	UHDRS	89	la
7	fluzole	placebo	HSG, 2003	CAG	poor effect	41	parallel	8 weeks	UHDRS	100	la
Dopa-agonists											
8	trans-Dihydroisuride	placebo	Stocchi, 1989	history	no effect	10	crossover	4 weeks	AIMS	58	lb
9	trans-Dihydroisuride	placebo	Bassi, 1986	clinic	positiv	10	crossover	2 weeks	self	63	lb
Others											
10	fluoxetine	placebo	Como, 1997	n.s.	no effect	12	parallel	4 months	TFC	71	lb
11	cannabidiol	placebo	Conroe, 1991	history	no effect	15	crossover	6 weeks	self	73	lb
Neuroprotection											
12	coenzyme Q10	remacemide, placebo	HSG, 2001	hist or CAG	trend	76	parallel	30 months	UHDRS	98	la
12	remacemide	coQ10, placebo	HSG, 2001	hist or CAG	no effect	66	parallel	30 months	UHDRS	98	la
13	remacemide	placebo	Kiebertz, 1996	history	safe	18	parallel	6 weeks	HDMRS	95	la
14	lamotrigine	placebo	Kremer, 1999	CAG	no effect	28	parallel	30 months	TFC, QNE	95	la
15	OPC-14117	placebo	HSG, 1998	history	safe	23	parallel	3 months	UHDRS	95	la
16	leibonone	placebo	Ranen, 1996	history	no effect	48	parallel	12 months	QNE	92	la
17	alpha-tocopherol	placebo	Peysser, 1995	history	no effect	40	parallel	12 months	QNE	95	la
18	halofen	placebo	Shoulson, 1989	history	no effect	23	parallel	30 months	TFC	91	la
19	minocycline	placebo	HSG, 2004	hist or CAG	safe	37	parallel	8 weeks	UHDRS	95	la
20	unsaturated fatty acids	placebo	Puri, 2005	hist or CAG	no effect	39	parallel	12 months	UHDRS	95	la

AIMS = Abnormal Involuntary Movement Scale, UHDRS = Unified HD Rating Scale, HDMRS = HD Motor Rating Scale, CSS = Chorea severity score; video = video-rating; self = subjective chorea quantification by the authors, QNE = Quantified Neurological Examination. TFC = total functional capacity.

n = number of patients on active drug who completed the study, study duration: the period that all patients underwent.

HD diagnosis: CAG = genetically proven; history = clinic and positive family history; clinic = clinical impression alone. HSG = Huntington study group.

la = study quality > 75%; lb = study quality < 75%.

[36], *phenothiazine* [37], *trifluoperazine* [32, 38], *per-phenazine* [39, 40], *chlorpromazine* [41], and *melperon* [42] were inconclusive regarding therapeutic benefits and/or their agents are out of use today.

In conclusion, low doses of conventional dopamine-blocking antipsychotics are often well tolerated and may ameliorate the severity of choreatic hyperkinesias, whereas high doses are rarely helpful and may impair oculomotor [43], orolingual [44], motor control and cognitive function. Moreover, these neuroleptics may accelerate functional decline [45] and may induce tardive dystonia [46]. Indeed, the severity of dystonia in HD has been associated with the use of an antidopaminergic agent [47], although this point needs further study. It is noteworthy that neuroleptic malignant syndrome, albeit being a known adverse effect of conventional antipsychotics, has never been reported in HD patients for this substance class.

A.2 Dopamine-Depleting Medications

Tetrabenazine is chemically related to antipsychotic drugs by causing a dopamine depletion of the presynaptic vesicles. It appeared effective in reducing chorea in seven out of eight small level-II double-blind studies [7, 31, 48-52]. Moreover, a myriad of level III trials [53-62] and case reports [63-65] mostly support antichoreatic efficacy of tetrabenazine in HD (for details see the tables). One recent retrospective level III study had to be excluded from our analysis due to unclear data presentation (analysis of HD inseparable in a pool with other chorea) [66]. Unfortunately, adverse reactions are frequent and limit the usefulness of tetrabenazine. They include sedation, insomnia, depression, anxiety, parkinsonism, dysphagia, akathisia, and, rarely, neuroleptic malignant syndrome [67-69]. Severe depression occurred in three of 11 HD patients under tetrabenazine, in one leading to a suicide attempt, in a single-blind cross-over

Table 2. Level II Studies 1965 – 2005

	active drug	Control substance	First author, year		HD diagnosis	Effect	n=	Randomized	Blinded	Study design	Study duration	HD score
Antipsychotic drugs												
1	haloperidol	-	Koller 1985	history	positiv	13	no	single	-	n.s.	video, self	
2	haloperidol	lithium, placebo	Leonard 1974, 75	history	no effect	6	yes	double	crossover	3 weeks	self	
3	haloperidol	tetrabenazine	Gimenez, 1989	clinic	positiv	11	no	single	crossover	11- days	Kartzinel, 1976	
4	fluphenazine	placebo	Terrence, 1976	n.s.	positiv	5	n.s.	double	parallel	4 weeks	self	
5	perphenazine	placebo	Fahn, 1972	clinic	positiv	8	n.s.	double	crossover	4 weeks	video, self	
6	tiapride	placebo	Chouza 1982	n.s.	positiv	2	no	double	crossover	2 weeks	self	
7	tiopropazate	tetrabenazine, placebo	McLellan, 1974	clinic	positiv	9	yes	double	crossover	2 weeks	video, self	
8	lozapine	placebo	Caïne, 1979	n.s.	poor effect	3	yes	double	crossover	4 weeks	n.s.	
Dopamin-depleting agents												
9	tetrabenazine	-	Ondo, 2002	CAG	positiv	18	no	single	-	2-11 months	AIMS, video	
10	tetrabenazine	placebo	Jankovic 1982	clinic	positiv	1	yes	double	crossover	3 weeks	video, self	
11	tetrabenazine	placebo	Asher, 1981	clinic	positiv	8	no	double	crossover	3 weeks	video, self	
12	tetrabenazine	-	Swash, 1972a	clinic	positiv	2	no	single	-	30 weeks	video, self	
13	tetrabenazine	amantadine	Swash, 1972b	clinic	positiv	7	no	double	crossover	2 weeks	video, self	
7	tetrabenazine	tiopropazate, placebo	McLellan, 1974	clinic	positiv	9	yes	double	crossover	2 weeks	video, self	
3	tetrabenazine	haloperidol	Gimenez, 1989	clinic	positiv	11	no	single	crossover	11- days	Kartzinel, 1976	
14	tetrabenazine	haloperidol	Gilligan, 1972	n.s.	poor effect	6	no	double	crossover	8 weeks	video, self	
NMDA-antagonists												
15	amantadine	tetrabenazine	Swash, 1972b	clinic	no effect	7	no	double	crossover	2 weeks	video, self	
16	amantadine, IV	placebo	Lucetti, 2003	CAG	positiv	9	yes	double	crossover	1 day	AIMS, UHDRS	
17	amantadine	placebo	Heckmann, 2004	CAG	no effect	7	yes	double	crossover	6 weeks	UHDRS	
18	tetamide	placebo	Murman, 1997	history	no effect	10	yes	double	crossover	1 day	UHDRS	
19	milacemide	placebo	Giuffra, 1992	history	no effect	7	no	double	crossover	3 days	AIMS	
GABA agonists												
20	L-acetyl-carnitine	placebo	Goetz, 1990	history	no effect	10	yes	double	crossover	1 week	AIMS	
21	soniazid	placebo	Manyam 1980, 81	87, 90	history	no effect	6	yes	double	crossover	6 weeks	AIMS, video
22	soniazid	placebo	Perry, 1982	history	no effect	9	no	double	crossover	4 months	video, self	
23	soniazid	placebo	McLean, 1982	clinic	no effect	8	yes	double	crossover	3 months	video, self	
24	GABA	baclofen	Fisher, 1982	n.s.	no effect	22	n.s.	double	crossover	6 months	video, self	
25	gamma-vinyl GABA	placebo	Scigliano, 1984	n.s.	no effect	6	yes	double	crossover	2 weeks	self	
26	THP	placebo	Foster, 1983	history	no effect	5	no	double	crossover	2 weeks	AIMS	
27	aminoxyacetic acid	placebo	Perry, 1980	history	no effect	7	no	single	crossover	15 weeks	video, self	
28	muscimol	placebo	Shoulson, 1978	clinic	no effect	10	no	double	crossover	1 week	video, self	
29	imidazole-4-acetic acid	placebo	Shoulson, 1975	n.s.	no effect	3	n.s.	double	parallel	4 weeks	self	
24	baclofen	GABA	Fisher, 1982	n.s.	no effect	22	no	double	crossover	6 months	video, self	
Dopa-agonists												
30	apomorphine	placebo	Albanese, 1995	history	positiv	9	no	double	crossover	1 day	DCRS-HD	
31	apomorphine	placebo	Corsini, 1978	n.s.	positiv	4	no	single	crossover	1 day	self	
32	apomorphine	placebo	Tolosa, 1974	history	positiv	4	n.s.	double	crossover	1 day	AIMS	
33	3KF 39393	placebo	Braun, 1989	history	no effect	5	no	double	crossover	1 day	AIMS	
34	promocriptine	placebo	Frattola, 1977	clinic	positiv	11	no	double	crossover	4 weeks	self	
35	promocriptine	placebo	Kartzinel, 1976	history	worsen	6	no	double	crossover	8 weeks	self	
36	suride	placebo	Frattola, 1983	history	positiv	11	no	single	crossover	1 day	ARS	
Others												
37	piracetam	placebo	Mateo, 1996	n.s.	worsen	11	no	double	crossover	1 day	self	
38	piracetam	placebo	Destee, 1984	history	worsen	6	n.s.	double	crossover	1 day	AIMS	
39	cysteamine	placebo	Shults, 1986	n.s.	no effect	5	yes	double	crossover	2 weeks	video, self	
40	FK 33-824	placebo	Agid, 1983	n.s.	no effect	12	yes	double	crossover	1 day	self	
41	thium	placebo	Vestergaard, 1977	history	no effect	6	yes	double	crossover	6 weeks	self	
42	thium	placebo	Aminoff, 1974	clinic	no effect	9	no	double	crossover	7 weeks	video, self	

(Table 2) contd....

	active drug	Control substance	First author, year		HD diagnosis	Effect	n=	Rando- mized	Blinded	Study design	Study duration	HD score
Others												
43	lithium	placebo	Carman, 1974	n.s.	no effect	6	n.s.	double crossover	3 weeks	self		
2	lithium	haloperidol, placebo	Leonard 1974, 75	history	no effect	6	yes	double crossover	3 weeks	self		
44	dimethylaminoethanol	placebo	Tarsy, 1977	n.s.	no effect	3	no	double crossover	2 weeks	self		
45	dimethylaminoethanol	placebo	Caraceni, 1978	history	no effect	9	yes	double crossover	40 days	video, self		
46	indolol	placebo	Greendyke, 1986	n.s.	positiv	1	yes	double crossover	2 weeks	self		
47	arecoline	placebo	Nutt, 1978a	clinic	worsen	6	yes	double crossover	1 day	self		
48	scopolamine	benztropine	Nutt, 1983a,b	history	worsen	4	yes	double crossover	1 day	self		
49	halrexone	placebo	Nutt, 1978b	n.s.	no effect	6	no	double crossover	1 day	self		
50	vitamin E	placebo	Caro, 1978	history	no effect	10	n.s.	double crossover	24 weeks	self		
51	physostigmin	placebo	Davis, 1978a,b	history	poor effect	6	no	single crossover	1 day	video, self		
52	choline	placebo	Davis, 1976	clinic	poor effect	4	no	single crossover	8 weeks	video, self		
53	creatine	placebo	Verbessem, 2003	CAG	no effect	26	no	double parallel	12 months	UHDRS		
Neuroprotection												
54	unsaturated fatty acids	placebo	Puri, 2002	n.s.	positiv	3	yes	double parallel	6 months	UHDRS		
55	unsaturated fatty acids	placebo	Vaddadi, 2002	CAG	positiv	9	yes	double parallel	6 months	UHDRS		

AIMS = Abnormal Involuntary Movement Scale, UHDRS = Unified HD Rating Scale, CSS = Chorea severity score, HDMRS = HD Motor Rating Scale,

DCRS-HD= David Clinical RS for HD, ARS= Arbitrary Rating Scale.

Video = video-rating; self = subjective chorea quantification by the authors. N= number of patients

on active drug who completed the study.

Study duration: the period that all patients underwent. n.s. = not stated

in the paper.

Table 3. Level III Studies 1965 – 2005

	Substance	First author, year	HD diagnosis	Effect	n=	Study design	Study duration	HD score		
Antidopaminergics										
1	haloperidol	Barr, 1988	history	positiv	10	open label	2 weeks	AIMS		
2	haloperidol (+others)	Girotti, 1984	history	positiv	9	open label	4 weeks	self		
3	haloperidol (+others)	Caraceni, 1977	n.s.	positiv	16	open label	2 weeks	video, self		
2	pimozide (+others)	Girotti, 1984	history	positiv	11	open label	4 weeks	self		
4	pimozide	Arena, 1980	n.s.	positiv	5	open label	4 months	self		
5	pimozide	Siegmund, 1982	history	positiv	11	retrospective	weeks - years	no rating		
6	pimozide	Bobon, 1968	n.s.	no effect	1	open label	6 months	no rating		
7	fluphenazine	Whittier, 1968	history	positiv	65	retrospective	8 weeks	self		
8	tiapride	Quinn 1985	n.s.	no effect	7	prospective	n.s.	n.s.		
2	tiapride (+others)	Girotti, 1984	history	no effect	12	open label	4 weeks	self		
9	melperon	Mattson, 1974	n.s.	no effect	7	open label	3 weeks	self		
10	clozapine	Colosimo, 1995	n.s.	poor effect	8	retrospective	av. 18 months	no rating		
11	clozapine	Bonuccelli, 1994	n.s.	positiv	5	open label	3 weeks	AIMS		
12	olanzapine	Paleacu, 2002	CAG or clinic	poor effect	9	open label	6 months	UHDRS		
13	olanzapine	Bonelli, 2002	CAG	positiv	9	open label	2 weeks	UHDRS		
14	olanzapine	Squitieri, 2001	CAG	poor effect	11	open label	6 months	UHDRS		
Dopamin-depleting agents										
15	tetrabenazine	Jankovic, 1997	n.s.	positiv	29	retrospective	av. 28 months	self		
16	tetrabenazine	Jankovic, 1988	n.s.	poor effect	10	retrospective	1-80 months	self		
17	tetrabenazine	Toglia, 1978	history	positiv	7	retrospective	2-10 months	video, self		
18	tetrabenazine	Huang, 1976	n.s.	poor effect	6	open label	9-18 months	self		
19	tetrabenazine	Astin, 1974	n.s.	positiv	26	retrospective	weeks - years	self		
20	tetrabenazine	McLellan, 1972	n.s.	poor effect	11	retrospective	1-12 months	self		
22	tetrabenazine	Pakkenberg, 1968	n.s.	poor effect	11	open label	> 2 months	self		

(Table 3) contd....

	Substance	First author, year	HD diagnosis	Effect	n =	Study design	Study duration	HD score		
Dopamin-depleting agents										
23	tetrabenazine	Dalby, 1969	n.s.	positiv	8	open label	1-4 weeks	video, self		
24	tetrabenazine	Kingston, 1969	n.s.	positiv	24	retrospective	1120 months	descriptive		
25	tetrabenazine + pimozide	Fog, 1970	n.s.	positiv	12	open label	2-7 months	descriptive		
NMDA-antagonists										
26	amantadine	Gray, 1975	n.s.	poor effect	6	open label	1-3 days	no rating		
27	amantadine	Lucetti, 2002	CAG	positiv	8	open label	12 months	AIMS, UHDRS		
28	amantadine	Scotti, 1971	history	poor effect	6	open label	2-6 months	no rating		
GABA agonists										
29	isoniazid	Stober, 1983	n.s.	poor effect	11	open label	3-17 months	TFC		
30	isoniazid	Perry, 1979	history	poor effect	6	open label	4-25 months	self		
31	isoniazid	Perry, 1977	n.s.	positiv	6	open label	2-16 months	self		
3	GABA (+others)	Caraceni, 1977	n.s.	no effect	3	open label	2 weeks	video, self		
32	L-glutamate	Barr 1978	n.s.	no effect	5	open label	3 years	self		
33	baclofen	Paulson, 1976	n.s.	poor effect	15	open label	>4 weeks	video, self		
Dopa-agonists										
34	apomorphine (+others)	Caraceni, 1980	n.s.	positiv	4	open label	1 day	video, self		
35	bromocriptine (+others)	Caraceni, 1980	n.s.	no effect	4	open label	3 weeks	video, self		
36	bromocriptine	Loeb, 1979	history	poor effect	10	open label	3-4 weeks	self		
37	bromocriptine	Albano, 1979	n.s.	positiv	11	open label	n.s.	n.s.		
Others										
38	donepezil	Fernandez, 2000	CAG	poor effect	8	open label	2x 6 weeks	UHDRS		
39	rivastigmine	de Tommaso, 2004	CAG	poor effect	11	open label	8 months	MMSE		
35	lysuride (+others)	Caraceni, 1980	n.s.	no effect	4	open label	3 weeks	video, self		
34	diazepam (+others)	Caraceni, 1980	n.s.	positiv	3	open label	1 day	video, self		
35	cyproheptadine (+others)	Caraceni, 1980	n.s.	positiv	3	open label	2 weeks	video, self		
3	diprophyllacetic acid (+others)	Caraceni, 1977	n.s.	no effect	4	open label	2 weeks	video, self		
3	CB 154 (+others)	Caraceni, 1977	n.s.	worsen	5	open label	2 weeks	video, self		
3	physostigmin (+others)	Caraceni, 1977	n.s.	no effect	4	open label	1 day	video, self		
40	dextromethorphan	Walker, 1989	history	no effect	11	open label	4-8 weeks	TFC		
41	dextromethasone	Nuti, 1991; Bonuccelli, 1992	history	positiv	6	open label	20 days	AIMS		
42	somatostatin	Dupont, 1978	n.s.	no effect	1	open label	1 day	self		
43	choline	Davis, 1976, 77, 78	n.s.	positiv	4	open label	1 day	video, self		
44	choline	Aquilonius, 1977	n.s.	no effect	5	open label	1 day	video, self		
45	lithium	Mattsson, 1973b	history	positiv	4	open label	3 weeks	self		
46	disulfiram	Mattsson, 1974	n.s.	no effect	5	open label	4 weeks	video, self		
Neuroprotection										
47	riluzole	Rosas, 1999	n.s.	positiv	8	open label	6 weeks	UHDRS		
48	riluzole	Seppi, 2001	CAG	positiv	9	open label	12 months	UHDRS		
49	minocycline	Bonelli, 2003	CAG	positiv	14	open label	6 months	UHDRS		
49	minocycline	Bonelli, 2004	CAG	positiv	11	open label	24 months	UHDRS		
50	minocycline	Thomas, 2004	CAG	no effect	30	open label	6 months	UHDRS		
51	coenzyme Q10	Feigin, 1996	n.s.	no effect	10	open label	6 months	HDRS		
522	coenzyme Q10	Koroshetz, 1997	n.s.	no effect	18	open label	> 2 months	MRS		
53	creatine	Tabrizi, 2003	CAG	no effect	13	open label	12 months	UHDRS		
53	creatine	Tabrizi, 2003	CAG	possible effect	9	open label	24 months	UHDRS		
54	creatine	Bender, 2003	CAG	no effect	20	open label	8 weeks	UHDRS		

AIMS = Abnormal Involuntary Movement Scale, UHDRS = Unified HD Rating Scale, CSS = Chorea severity score, TFC = , QNE = ADL = , HDMRS = HD Motor Rating Scale, DCRS-HD = David Clinical RS for HD, ARS = Arbitrary Rating Scale, MMSE = Mini Mental State Examination n = number of patients on verum who completed the study
 study duration: the period that all patients underwent
 MRS = Magnetic Resonance Spectroscopy

Table 4. Therapeutic case reports on HD 1965 – 2005.

Typical Antipsychotics				n=			
1	haloperidol	Kwalo 1970	chorea	2	effective		
2	haloperidol (& amantadine)	Saran 1980	chorea	2	effective		
3	haloperidol & lithium	Manyam 1973	chorea	1	effective		
4	fluphenazine	Koreyi 1967	chorea	2	effective		
5	tetrabenazine & pimozide	McArthur 1976	chorea	3	effective		
6	tetrabenazine	Soutar 1970	chorea	3	effective		
7	sulpiride	Knwling 1991	chorea	1	effective		
8	pimozide (+others)	Lal 1973	chorea	2	no effect		
9	trifluoperidol	Targhati 1968	chorea	4	effective		
10	melperon	Matsson 1974	chorea, psychosis	3	some effect		
Atypical Antipsychotics							
11	clozapine	Vallette 2001	chorea	1	effective		
12	clozapine	Sajatovic 1991	chorea, psy. depression	1	effective		
13	olanzapine	Laks 2004	chorea, behavior	1	effective		
14	olanzapine	Jimenez 2002	chorea	2	effective		
15	olanzapine	Bonelli 2002a	chorea	1	effective		
16	olanzapine & riluzole	Bonelli 2002b	chorea	2	effective		
17	olanzapine	Bogemann 2001	chorea	1	effective		
18	olanzapine, valproate	Grove 2000	chorea, aggression	2	effective		
19	olanzapine	Dipple 1999	chorea	1	effective		
20	olanzapine	Etchebehere 1999	chorea	1	effective		
21	risperidone	Erdemoglu 2002	psychosis, chorea	1	effective		
22	risperidone	Madhusodanan 1998a, b	psychosis	1	effective		
23	risperidone	Parsa 1997	chorea	1	effective		
24	risperidone	Dalocchio 1999	chorea	4	effective		
25	ziprasidone	Bonelli 2003a	chorea	3	effective		
26	quetiapine	Bonelli 2002c	chorea	1	effective		
27	zotepine	Bonelli 2003b	chorea	1	effective		
Dopa-agonists & Glutamate-antagonists							
28	pramipexole	Bonelli 2002d	rigidity	1	effective		
29	amantadine	Magnet 2004	rigidity	1	effective		
30	amantadine (+L-dopa)	Bird 1971	rigidity	1	no effect		
31	L-dopa	Racette 1998	rigidity	1	effective		
32	L-dopa	Reuter 2000	rigidity	4	effective		
33	L-dopa (+amantadine)	Bird 1971	rigidity	1	effective		
34	L-dopa	Tan, 1972	chorea	1	effective		
35	L-dopa	Schenk 1974	chorea	2	effective		
8	L-dopa (+others)	Lal 1973	chorea	2	worsen		
8	apomorphine (+others)	Lal 1973	chorea	2	no effect		
36	bromocriptine	Tsunizumi 1994	chorea	1	effective		
16	riluzole & olanzapine	Bonelli 2002b	chorea	2	effective		
37	riluzole & olanzapine	Bonelli 2002c	chorea	1	effective		
38	riluzole	Bodner 2001	chorea	1	effective		
2	amantadine (& haloperidol)	Saran 1980	chorea	2	no effect		
Antidepressives							
39	mirtazapine	Bonelli 2003c	depression	1	effective		
40	sertraline	Ranen, 1996	aggression	2	effective		
41	sertraline	Patzold, 2002	obsessive disorder	1	effective		
42	paroxetine	Royuela Rico, 2003	obsessive disorder	1	effective		
43	fluoxetine, L-deprenyl	Patel 1996	depression	1	effective		
44	fluoxetine	De Marchi 2001	agitation	2	effective		
45	fluoxetine	De Marchi 2001	chorea	2	effective		
46	fluoxetine	Chari 2003	chorea	1	worsen		
47	amitriptyline	Folstein 1983	depression	10	effective		

(Table 4) contd....

Antidepressives						
48	amitriptyline (+diazepam)	Caine 1983	anxiety	2	effective	
49	MAO-I	Ford 1986	depression	3	effective	
50	amoxapine	Moldawsky 1984b	depression, dysarthria	1	effective	
Others						
51	propranolol	Stewart 1993	hypomania	1	effective	
52	propranolol	Stewart 1987	aggression	3	effective	
53	medroxyprogesterone acetate	Bass 2001	sexual dishibition	1	effective	
54	carbamazepine	Cohen 2000	dysuria	3	effective	
55	lithium + baclofen	Anden 1973	chorea	2	worsen	
56	lithium	Dulen 1973	chorea	6	effective	
57	lithium	Mattsson 1973a	chorea	2	effective	
58	nabilone	Müller-Vahl 1999	chorea	1	worsen	
59	leuprolide	Rich 1994	exhibitionism	1	effective	
60	(-)-OSU6162	Tedroff 1999	chorea	1	effective	
61	pyridoxine	Braham 1981	chorea	2	no effect	
62	rivastigmine	Rot, 2002	dementia	3	no effect	
63	minocycline	Denovan-Wright 2002	chorea, psychiatry	1	effective	
64	clonazepam	Stewart 1988	chorea	1	effective	
65	clonazepam	Petris 1976	chorea	3	effective	
66	clonazepam	Novom 1976	intention myoklonus	1	effective	
67	bupiron	Bhandary 1997	aggression	1	effective	
68	bupiron	Byrne 1994	aggression	1	effective	
69	bupiron	Findling 1993	aggression	2	effective	
70	diazepam, amitriptyline	Caine 1983	anxiety	2	effective	
71	diazepam	Farrell 1968	chorea	1	effective	
72	valproate	Symington 1978	chorea	3	no effect	
73	valproate	Tan, 1976	chorea	1	no effect	
74	valproate	Vogel 1991	myoclonus	2	effective	
75	valproate	Kereschi 1980	myoclonus	1	effective	
76	valproate	Previdi 1980	myoclonus	1	effective	
77	dimethylaminoethanol	Amsterdam 1974	chorea	1	effective	
78	botulinum to xine	Nash 2004	bruxism	1	effective	
79	levetiracetam	Zesiewicz 2005	chorea	1	effective	

Table 5. Case reports on adverse effects in HD patients 1965 - 2005.

tetrabenazine	Osseman 1996	1	neuro. malignant syndrome
tetrabenazine	Burke 1981	1	neuro. malignant syndrome
tetrabenazine	Mateo 1992	1	neuro. malignant syndrome
tetrabenazine	Snaith 1974	4	dysphagia, 3 deaths aspiration
olanzapine	Bonelli 2003	1	seizure
olanzapine	Benazzi 2002	1	tardive dyskinesia
amantadine	Stewart 1987a	2	aggression
propranolol	Stewart 1987b	1	aggressiveness
pindolol	von Hafften 1989	1	aggressiveness
levetiracetam	Zesiewicz 2005	1	parkinsonism, lethargy

level-II study [7]. Snaith and Warren [70] reported severe dysphagia in four HD patients on tetrabenazine, leading to death from aspiration pneumonia in three of them. In contrast to traditional neuroleptics, neuroleptic malignant syndrome has been reported three times in HD patients due to the use of tetrabenazine [67-69] (see Table 5). For these rea-

sons, the substance is not currently approved by the Food and Drug Administration and is available in the USA only as an investigational drug (www.fda.gov). *Reserpine* [71-78], a chemically equivalent dopamine depleting drug, has fallen into disfavor due to its numerous and grave adverse reactions [79].

A.3 Atypical Antipsychotic Drugs

Atypical antipsychotic drugs have not been evaluated in level-I or level II trials (with the exception of clozapine), but they represent novel agents for treating movement disorders associated with HD. Whereas behavioral subscores (primary outcome measure) improved with low doses (5 mg/d) in two level III studies [80, 81] of *olanzapine*, higher doses (up to 30 mg/d) significantly ameliorated not only chorea, but also orolingual dysfunction, finger dexterity, and gait in a level III study [82]. A series of case reports confirm the latter results [83-90]. However, unfortunately, a case of seizure [91] and tardive dyskinesia [92] in HD have been described. Even less documented, *risperidone* appears to be helpful for the treatment of HD associated psychosis [93-95] and chorea [93, 96, 97] in a series of case reports. Motor function of the Unified HD Rating Scale (UHDRS) has been shown to significantly improve with *quetiapine* [98], *zotepine* [99], and *ziprasidone* [100] in further case reports. Interestingly, a recent case report suggests drug holidays in atypical antipsychotics when the antichoreatic effect wanes [101].

In contrast to the other atypicals, *clozapine* is better documented, but has less effect. It showed poor symptomatic effects in a level-Ib trial with 33 patients [102]; moreover, adverse reactions (drowsiness, fatigue, anticholinergic symptoms, and walking difficulties) forced trial termination in six patients and dose reduction in another eight. A level-II [103] and a level III study [104] revealed similar results. However, another level III study [105] and a case report [106] found positive effects on chorea. There is also a positive case report on psychotic depression, successfully treated with clozapine [107]. Anyway, the serious adverse effect of leucopenia makes clozapine less feasible for HD patients, who are especially prone to noncompliance due to behavioral symptoms.

A.4 Glutamate Antagonism

In the last decade, the "excitotoxin theory" suggested, that neurodegeneration in HD is caused by a relative excess of excitatory neurotransmitters such as glutamate [108]. For this reason, several NMDA-receptor antagonist were tested for a symptomatic or even neuroprotective effect. However, *ketamine* [109], or *milacemide* [110] did not show any symptomatic effect in level II studies. Moreover, ketamine caused a decline in memory and verbal fluency in the ten patients tested [109]. In a high-quality, level-I paper, Verhagen-Metman *et al.* [111] could show that *amantadine* (400 mg/d) lowered chorea scores, with a median reduction in extremity chorea at rest of 36% for all 22 evaluable patients. Parkinsonian rating scores did not worsen in this study, there was no consistent change in cognitive measures, and adverse event profile was benign. These data were confirmed by a level-II study of a 2-hour IV infusion of amantadine or placebo to nine patients with HD on two different days [112] and a level-III paper from the same authors [113]. However, in contrast, in a high-quality, level-I randomized placebo-controlled crossover trial with 2 weeks of treatment, O'Suilleabhain and Dewey [114] did not observe any effect of amantadine (300 mg/d) on chorea of HD patients, confirmed by two level-II studies [51, 115], two level-III papers [116, 117] and a case reports [15]. Moreover, amantadine may increase irritability and aggressiveness in HD patients

[118], although Heckmann and coworkers recently found an (not significant) improvement in the behavioral scores of HD patients [115]. In summary, there is inconclusive evidence for or against the use of amantadine in HD chorea. *Remace-mide* was shown to be a safe drug in a tolerability study [124]. Thereafter, the Huntington Study Group examined its benefits [125]. Unfortunately, it did not significantly alter the decline in total functional capacity of the UHDRS (i.e. no neuroprotective effect), although it tended to have a beneficial impact on the chorea subscale of the UHDRS (i.e. some symptomatic effect).

Riluzole is the most promising substance in this group. It was tested in an 8-week double-blind dose-ranging level I multi-center study [119]. The authors could show that, whereas riluzole 100 mg/day did not change chorea, riluzole

200 mg/day somewhat ameliorated chorea without improving functional capacity or other motor, cognitive, behavioral, or functional components of the UHDRS. These results are comparable to those of sulpiride [4]. In fact, the mean reduction of the UHDRS chorea score (range 0 – 28 units) was 2.2 units - a difference only statisticians can observe. Unfortunately, only few of the dopamine antagonist studies use the UHDRS and are therefore comparable, but olanzapine reduced the same chorea score for 6.5 units in a open label study [82]. Riluzole probably fails to be sufficiently potent to treat moderate and severe chorea - and mild chorea needs no treatment. For this reason, the outcome of this study was considered "poor effect" in Table 1, despite a significant amelioration of chorea. Moreover, treatment was accompanied by liver transaminase abnormalities that would require monitoring in long-term studies [119]. Two level-III studies

[120, 121] found transient antichoreatic effects (i.e. not significant after one year of treatment) and more sustained effects on psychomotor speed and behavior. Three more case reports with positive effects on chorea have been published

[85, 122, 123]. A European level-I trial is currently under-way.

A.5 GABAergic Therapy

As GABA, an inhibitory neurotransmitter, is decreased in HD brains [126] and CSF [127], three main groups of agents have been tried to enhance GABAergic neurotransmission in HD. These include the GABA precursors, such as glutamate, GABA mimetic drugs, such as gammavinyl-GABA, muscimol, THIP (4,5,6,7-tetrahydroisoxazolo-{5,4,-c} pyridin-3-ol), or baclofen, and GABA transaminase inhibitors, such as isoniazid. *Isoniazid* significantly elevated both free and conjugated GABA levels in human CSF [128] but was ineffective in HD in several level-II trials [129-134] and level-III studies [135-137]. *Gamma-vinyl GABA* [138], *THIP* (4,5,6,7-tetrahydroisoxazolo-(5,4,-c) pyridin-3-ol) [139] *L-acetyl-carnitine* [140] *aminoxyacetic acid* [141], and *muscimol* [142] were shown to be ineffective in small level-II trials (10 or less patients). *Baclofen* was found to be beneficial as an antichoreic agent in a level-III [143] and a case report (combined with lithium) [144] but failed to show efficacy in a larger level-I study [145]. Also *valproate*, which is thought to elevate brain GABA levels, had no beneficial effect on involuntary movements in two case reports [146, 147]. In an attempt to augment GABA-mediated neurotransmission, *L-glutamate* (the substrate for glutamic acid

decarboxylase) and pyridoxine, its cofactor, were given in an open label trial to five patients for two years without motor or behavioral effect [148]. Interestingly, *levetiracetam* markedly reduced chorea, but induced parkinsonism and lethargy in a HD patient [149].

Benzodiazepines act at the GABA-benzodiazepine receptor complex in the brain to enhance GABA action, possess anxiolytic, sedative, hypnotic and anticonvulsant properties [79] and may therefore afford nonspecific suppression of hyperkinesias in HD patients. However, the clinical use of benzodiazepines in HD is poorly documented. Available case reports are based on some patients receiving *clonazepam* [150, 151], *diazepam* [152, 153], or *chlordiazepoxide* [154, 155].

A.6 Other Agents for the Treatment of Chorea

Interestingly, *apomorphine* proved to be effective in several level-II [156-158], level-III trials [159], and case reports [28]. Low dose apomorphine may result dopaminergic autoreceptor stimulation with consequent inhibition of dopamine release. We have two conflicting level-II trials on *bro-mocriptine*, one positive [160], one negative [161]. Lower evidence level papers on bromocriptine are divided as well [159, 162-164]. Studies on other antidopaminergic agents like *trans-Dihydroxylisuride* [165, 166], *lisuride* [159, 167], and *SKF-39393* [168] are inconclusive.

Negative results for the treatment of chorea were found in level-Ib treatment trials with *fluoxetine* [169] and *cannabidiol*, a constituent of Cannabis [170]. We found negative level-II trials on the somatostatin-depleting agent *cysteamine* [171], the methionine-enkephalin analogue *FK 33-824* [172] and *lithium* [9, 13, 173-176] (for lithium also exist lower evidence papers with different results [144, 177-179]). *Piracetam* [180, 181] even worsened chorea in two level II trials of 1 day, respectively. *Choline* [182-185], the immediate precursor of acetylcholine, and *prednisolone* [186] (2 patients for 10 weeks), were mostly clinically inefficient in decreasing chorea in open label trials. Other investigated substances [187-207] are listed in Tables 2-4. In the 50es, several papers studied *procainamide*, an antiarrhythmic agent [208-213]. A remarkable case report on (-)-*OSU6162* [214], which belongs to a novel class of functional modulators of dopaminergic systems, with long-lasting improvement in a patient with HD should be mentioned at last in this section.

B. Treatment of other Neurological Features

As functional capacity worsens, chorea lessens, and dystonia intensifies [47, 215]. The prevalence of dystonia in HD of any severity is more than 80% [47]; approximately 12% of the patients suffer from dystonia-predominant HD [216]. Although the dystonia is not bothersome to most HD patients, it may cause functional impairment in others and then requires therapeutic intervention. Generally, treatment of dystonia is difficult and largely ignored in HD research. Astonishingly, HD dystonia has never been primary endpoint of any pharmacological intervention. Some trials evaluating *amantadine* [111], *riluzole* [120, 121], or *olanzapine* [82] in HD employed the UHDRS as outcome measure and were unable to show significant improvement of dystonia-subscores. Gait disorder in HD significantly decreases the

patient's quality of life and level of independence. Its clinical characteristics include a wide-based gait, lateral sway, spontaneous knee flexion, variable cadence, and parkinsonian features [217, 218]. Pharmacological intervention in HD gait disorders has rarely been studied so far. *Haloperidol* treatment decreased chorea but did not affect gait patterns in a level-II trial with 13 HD patients [8]. However, a small and short level-III study with high-dose *olanzapine* [82] achieved significant (35%) amelioration of UHDRS defined gait dysfunction (gait, tandem walking, and retropulsion pull test) in 9 HD patients. Other drugs have not been studied so far.

Rigidity & akinesia are a major source of motor disability in the akinetic-rigid Westphal variant of HD [219]. Anti-parkinsonian benefits were induced by *levodopa* [220-222] (up to 1000 mg/day) and *pramipexole* [223] (usual dose scheme) in open label case reports or case series. *Aman-tadine* and was helpful in a recent case report [224], whereas failed to be successful in an older report [220]. Although bradykinesia is a major feature of adult HD [225], it has never been a target for therapeutic intervention. Epilepsy is especially frequent in the Westphal-variant, however, it may also occur in adults with HD [226]. Several HD patients with epilepsy and myoclonus responded to treatment with *valproate* [227-229] or *clonazepam* [230]. Urinary incontinency is a major, widely ignored problem of late-stage HD [231] and is usually caused by a detrusor hyperreflexia. It was reported to respond to *carbamazepine* (200 mg/day) in three HD patients [232]. Bruxism was treated successfully with *botulinum toxin* in one patient [233].

TREATMENT OF PSYCHIATRIC SYMPTOMS

The behavioral assessment of the UHDRS comprises mood, low self-esteem/guilt, anxiety, suicidal thoughts, disruptive or aggressive behavior, irritable behavior, obsessions, compulsions, delusions, and hallucinations [234]. These are the main psychiatric challenges in clinical practice. No single level-I or level-II study has been carried out in this field.

Depression

The most frequent psychiatric onset symptom in HD is depression, often starting as isolated symptom [235]. There is evidence for postulating an "organic depression" in HD: a significantly lower metabolic activity in the basal ganglia and cingulate cortex is found in depressed as compared to nondepressed HD patients [236]. Despite the prevalence of depression among HD patients, only case reports are available on the use of antidepressants in this disorder. Positive results were reported for *amitriptyline* (n=10) [237], *imipramine* (n=1) [238, 239], *fluoxetine* (n=1) [240], *phenelzine* (n=2) [241], *isocarboxazid* (n=1) [241], *amoxapine* (n=1) [242], and *mirtazapine* (n=1) [243]. Finally, a case of psychotic depression was successfully treated with *clozapine* [107]. Controlled trials on antidepressants in HD are urgently required.

Psychotic Symptoms

Psychotic symptoms seem to be quite common in HD patients [244, 245]. A review of eleven studies of HD pa-

tients [246] found psychosis to be present in 3% to 12% of patients, ranging from nonspecific paranoia to presentations similar to schizophrenia. However, only two case studies on risperidone in psychotic symptoms are available [93, 95]; they report clinical improvement.

Behavioral Disorder

Increased irritability, lack of control and aggression are probably all related to frontal lobe dysfunction. Irritability and emotional dyscontrol are common in patients with HD and can cause great disturbance in their families or living situation. In male patients, crime rates are significantly increased compared to first degree relatives and controls [247]. *Haloperidol* was useful in a level-II study (double-blind, crossover in 6 patients) in treating irritability, aggressive outbursts, and depression [13]. Two small level-III studies on *olanzapine* [80, 81] showed a significant improvement in the UHDRS psychiatric subscores depression, anxiety, irritability, and obsessions. None of the patients reported side effects. Stewart reported efficacy of *propranolol* for aggressiveness in one patient [248], although he himself published a paradoxical aggressive effect of propranolol in a patient with HD [249] (a similar case was published with pindolol [250]). Other case reports concern *sertraline* [251] *fluoxetine* [201], *olanzapine* combined with *valproate* [87], and *bupirone* [252-254]. However, severe behavioral disturbance need a multimodality treatment schedule [255]. 82% of HD patients have one or more sexual disorders by DSM-III-R criteria [256], most commonly sexual hypoactivity although some patients may exhibit hypersexuality. There are only data from case reports available on treatment of hypersexuality in HD. A patient with HD and exhibitionism was successfully treated with *leuprolide*, a gonadotropin-releasing hormone agonist [257]. Another group used *medroxyprogesterone* to reduce hypersexuality [255].

Dementia

Dementia is one of the three cardinal clinical features in HD. Prevalence depends on the clinical stage of the disease. Even asymptomatic gene-carriers may reveal mild neuropsychological deficits. There is no level-I dementia treatment available for HD patients. *Choline esterase inhibitors* proved ineffective in level-III trials [258, 259] and a case report [260]. However, *unsaturated fatty acids* [262], *riluzole* [120], and *minocycline* [263] have shown to provide mild cognitive benefits (secondary endpoints) in open label trials.

Other Psychiatric Symptoms

HD patients with obsessive or compulsive symptoms show significantly greater impairment on neuropsychological tests measuring executive function than those without such symptoms [264]. In two case reports, the efficacy of *sertraline* [265] and *paroxetine* [266] for ameliorating obsessive behavior in HD have been shown. Level-III evidence on *olanzapine* [80, 81] for obsessions in HD has been mentioned earlier. Anxiety, on the other side, was described to be treated with *diazepam* and *amitriptyline* [267] in a case report. *Propranolol* was helpful in a HD patient with hypomania [268].

D. Neuroprotective Treatment Strategies

The discovery of the HD gene and its product, huntingtin, has improved understanding of the disease process and opened new approaches to interventional treatments [269-272]. Recent studies using transgenic mouse and *Drosophila* models have helped resolve some of these issues and raise hopes for development of therapeutic targets [273-275]. Most neuroprotective studies to date have employed interventions that attenuate or modulate glutamatergic neurotransmission, enhance bioenergetic mechanisms, or exert anti-oxidative properties [3].

Based on the evidence that *creatine*, like coenzyme Q10, enhanced mitochondrial oxidative functions defective in HD, and motivated by positive results in the transgenic mouse model, Tabrizi and coworkers undertook an open label study of nine HD patients on creatine [276, 277]. After 24 months of creatine treatment, there was no significant deterioration in the UHDRS (TMS, functional capacity scores, or neuro-psychological testing), which actually should be expected after 2 years. In a second short-term level III study, Bender *et al.* did not find any motor effect, but noted a change in brain metabolite levels after 8 weeks of treatment, measured by proton magnetic resonance spectroscopy [278]. Unfortunately, a level II (not randomized) 1-year double-blind placebo-controlled trial of creatine in 41 patients with HD (stage I through III) came to other results [279]. Scores on the functional checklist of the UHDRS, maximal static torque, and peak oxygen uptake decreased from the start to the end of the study in both groups, independent of the treatment received.

Highly *unsaturated fatty acids* were found to be effective in two small, short, double-blind, placebo-controlled studies [261, 262]. The rationale was based on the role of highly unsaturated fatty acids in cell membrane function, which may affect the propensity of a cell to undergo apoptosis and so may be effective in slowing the rate of neuronal cell death, both within and outside the striatum in HD [271]. However, as the number of treated patients was small (three and nine, respectively), these results must be treated with caution. Unfortunately, a recently published Level-I trial in 61 HD patients is inconsistent with these prior findings [280]. The authors did not find a significant difference between unsaturated fatty acids and placebo for the motor score. However, some subanalysis give reason to hope. Anyway, even larger level I studies are underway.

Minocycline, an inhibitor of caspase and neuronal apoptosis, has been demonstrated to delay disease progression, and extend survival by 14% in the R6/2 transgenic mouse model of HD [281, 282]. The first open-label pilot study on minocycline in HD [263] showed a significant amelioration in several motor capacities as well as cognitive parameters after 6 months. After 2 years [283], patients exhibited stabilization in general motor and neuropsychological function at endpoint, unlike the expected natural course of HD suggests. Moreover, a significant amelioration of psychiatric symptoms was present after 24 months. In contrast, a similarly designed level III study failed to find any effect after six months [284]. A safety and tolerability study found minocycline well tolerated and safe in HD patients [285], a level I clinical study is underway in the USA. An interesting case

Table 6. Conclusion on HD Chorea.

Substance	effective					poor/not effective					Efficacy Conclusions	Safety	Implications for Clinical Practice	
	Ia	Ib	II	III	cr	Ia	Ib	II	III	cr				
Antidopaminergics														
haloperidol		2	3	3		1					insufficient evidence	acceptable risk without monitoring	possibly useful	
fluphenazine			1	1							insufficient evidence	acceptable risk without monitoring	possibly useful	
sulpiride				1							unlikely efficacious	acceptable risk without monitoring	efficacy unlikely	
tiapride	1	1					2				insufficient evidence	acceptable risk without monitoring	investigational	
pimozide			4					1			insufficient evidence	acceptable risk without monitoring	investigational	
clozapine			1			1	1				unlikely efficacious	acceptable risk with monitoring	efficacy unlikely	
tetrabenazine	7	4	1			1	4				insufficient evidence	insufficient evidence	investigational	
olanzapine			1	8							insufficient evidence	acceptable risk without monitoring	possibly useful	
NMDA-antagonists														
amantadine	1		1		1	2	2	1			insufficient evidence	acceptable risk without monitoring	investigational	
ketamine						1					insufficient evidence	insufficient evidence	efficacy unlikely	
milacemide						1					insufficient evidence	insufficient evidence	efficacy unlikely	
riluzole			2	3	1						non-efficacious	acceptable risk with monitoring	investigational	
GABA agonists														
L-acetyl-carnitine						1					insufficient evidence	insufficient evidence	efficacy unlikely	
isoniazid			1			3	2				insufficient evidence	insufficient evidence	efficacy unlikely	
GABA						2	1				insufficient evidence	insufficient evidence	efficacy unlikely	
THIP						1					insufficient evidence	insufficient evidence	efficacy unlikely	
aminooxyacetic acid						1					insufficient evidence	insufficient evidence	efficacy unlikely	
muscimol						1					insufficient evidence	insufficient evidence	efficacy unlikely	
baclofen						1	1				insufficient evidence	acceptable risk without monitoring	efficacy unlikely	
Dopa-agonists														
apomorphine		3	1	1							insufficient evidence	acceptable risk with monitoring	investigational	
SKF 39393						1					insufficient evidence	insufficient evidence	efficacy unlikely	
trans-Dihydroisuride					1						insufficient evidence	insufficient evidence	efficacy unlikely	
bromocriptine	1		1			1	2				insufficient evidence	insufficient evidence	efficacy unlikely	
lisuride		1					1				insufficient evidence	acceptable risk without monitoring	efficacy unlikely	
Others														
fluoxetine											unlikely efficacious	acceptable risk without monitoring	efficacy unlikely	
cannabidiol											unlikely efficacious	insufficient evidence	efficacy unlikely	
FK 33-824						1					insufficient evidence	insufficient evidence	efficacy unlikely	
lithium			1	1		4		1			insufficient evidence	acceptable risk with monitoring	efficacy unlikely	
cysteamine											insufficient evidence	insufficient evidence	efficacy unlikely	
piracetam						2					insufficient evidence	acceptable risk without monitoring	efficacy unlikely	
Neuroprotection														
coenzyme Q10					1		2				unlikely efficacious	insufficient evidence	investigational	
remacemide					1						non-efficacious	insufficient evidence	not useful	
lamotrigine					1						non-efficacious	insufficient evidence	not useful	
idebenone					1						non-efficacious	insufficient evidence	not useful	
alpha-tocopherol					1						non-efficacious	insufficient evidence	not useful	
baclofen					1						non-efficacious	acceptable risk without monitoring	not useful	
unsaturated fatty acids	2										non-efficacious	insufficient evidence	investigational	
minocycline			1	1			1				insufficient evidence	acceptable risk without monitoring	investigational	
creatine						1	2				insufficient evidence	insufficient evidence	efficacy unlikely	

report is available showing persistent beneficial effects of minocycline for more than 1 year in one HD patient. Cessation of minocycline for 3 weeks resulted in an exacerbation of symptoms [286].

The lipophilic free-radical scavenger *OPC-14117* [287] was shown to be a safe drug in a 3 months, level-Ia RCT (n=23 on active drug) although no benefit on motor or cognitive function was observed. Elevations of hepatic trans-

minase in several subjects treated with OPC-14117 emphasized the need for adequate safety and tolerability studies before embarking on long-term neuroprotective trials. Two more label I clinical trials on free-radical scavengers have been carried out. A placebo-controlled trial of **alphatocopherol** [288] for one year in 73 HD patients (n=40 on active drug) did not show benefits. A label I trial on the anti-oxidant **idebenone** [289] in 91 HD patients (n=48 on active drug) over one year also failed to show any beneficial impact on the progression of HD.

Three label-Ia studies pursued anti-glutamatergic strategies. Baclofen and lamotrigine are thought to diminish glutamate neurotransmission by inhibiting corticostriatal glutamate release. However, a placebo-controlled trial of **baclofen** [145] in 60 patients for up to 42 months and a placebo-controlled trial of **lamotrigine** [290] in 64 patients followed for 30 months failed to show any benefit to the progression of the functional decline in HD. The Huntington Study Group examined the effect of the glutamate antagonist

remacemide and the enhancer of bioenergetics, **coenzyme Q10** [125] after remacemide turned out to be safe in a safety level I trial [124] and coenzyme Q10 was tested in two level III open-label trials [291, 292]. The authors conducted a multicenter, parallel group, double-blind, 2 x 2 factorial, randomized clinical trial. 347 HD patients were randomized to receive coenzyme Q10 300 mg twice daily, remacemide hydrochloride 200 mg three times daily, both, or neither treatment, and were evaluated every 4 to 5 months for a total of 30 months on assigned treatment. However, neither intervention significantly altered the decline in total functional capacity of the UHDRS, although patients treated with coenzyme Q10 showed a trend toward slowing in total functional capacity decline over 30 months.

CONCLUSION

This is the first EBR of drug therapy in HD. We hope that our summary of all pharmacological studies since 1965 (and most of them from 1950 to 1964) will guide the clinical

Table 7. Conclusion on other HD Symptoms

Substance	effective					poor/not effective					Implications for Clinical Practice	
	Ia	Ib	II	III	cr	Ia	Ib	II	III	cr		
Parkinsonian symptoms												
L-dopa				3								possibly useful
pramipexole				1								possibly useful
amantadine				1					1			investigational
Myoclonus / seizures												
valproate				3								possibly useful
clonazepam				1								possibly useful
Depression												
amitriptyline			1									possibly useful
mirtazapine				1								possibly useful
Psychosis												
risperidone				2								possibly useful
Behavioral disorder												
haloperidole		1										possibly useful
olanzapine			2	1								possibly useful
propranolole				1					1			investigational
buspirone				3								possibly useful
Hypersexuality												
leuprolide				1								possibly useful
medroxyprogesterone				1								possibly useful
Obsessions												
olanzapine			2									possibly useful
sertraline				1								possibly useful
paroxetine				1								possibly useful
Dementia												
CE-Inhibitors								2	1			efficacy unlikely
unsaturated fatty acids			1		1			1				not useful
minocycline				1								possibly useful
riluzole				1								possibly useful

cians in optimizing their choice of therapy in individual patients. Actually, there is poor evidence in management of HD today. The analysis of the twenty level-I studies fails to result in any treatment recommendation of clinical relevance.

Table 6 and 7 might serve as the conclusive summary of this review. All substances mentioned in Table 6 defined the motor function (mostly chorea) as their primary outcome measure. Surprisingly, no single dopamine antagonist is considered "efficacious" or at least "likely efficacious" according to the current evidence-based-medicine standards. This is easily explained by the fact that they all lack level Ia trials. Most of them even lack any level Ib trials (e.g. haloperidol, fluphenazine, tetrabenazine, olanzapine). Others drugs have been studied in level Ib trials, but with conflicting (tiapride) or even negative (sulpiride, clozapine) results. Due to the very methodology of a EBR, substances that would be considered the strongest antichoreatic agents by the vast majority of clinicians today have to be classified to have "insufficient evidence" with regard to their efficacy. For the daily practice, there is some evidence for treating chorea with haloperidole or fluphenazine, and less evidence for olanzapine. These three drugs have been considered to be "possibly useful" for the treatment of chorea in this analysis. Other substances (e.g. amantadine, riluzole, tetrabenazine, etc.) are considered "investigational" for chorea, i.e. the available evidence is insufficient to support the use of the intervention in clinical practice, but further study is warranted.

There is very poor evidence today for the treatment of psychiatric disturbances or dementia, the other two parts of the clinical trias of HD (see Table 7). Substances with trials on these targets would all necessarily be classified as "insufficient evidence". "Possibly useful" drugs for the clinical practice would be L-dopa and pramipexole for rigidity; amitriptyline and mirtazapine for depression; risperidone for psychosis; and olanzapine, haloperidol, and buspirone for behavioral symptoms in HD.

For the neuroprotective agents, it is even harder to make an appropriate judgment, possibly due to the complex methodology (how to proof neuroprotection?). The coenzyme Q10 data could be interpreted somewhat differently as we did in this paper, as well as the data on unsaturated fatty acids. There still is hope that these two substances are demonstrated effective with highly-powered studies. Three substances are considered "investigational" for possible neuroprotection in this paper: coenzyme Q10, minocycline, and unsaturated fatty acids.

In fact, EBRs emphasize efficacy studies. Sometimes there is a discrepancy between information provided by studies focused on efficacy and the simple clinical reality (effectiveness). The level-Ia paper on riluzole makes the dilemma somewhat visible. In some illnesses, real world treatment and evidence-based information are slowly converging. In other illnesses, like HD, patients are treated with medications with very limited evidence to support them. For many of the problems arising in HD, the recommended treatment may have limited evidence-based support - due to our limited knowledge in this area. Treatment for HD may still rest more on the common sense of physicians than in the information provided by the literature.

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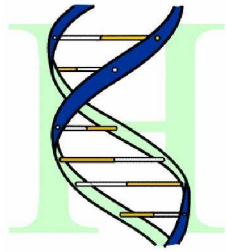
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FORME JUVÉNILE DE LA MALADIE DE HUNTINGTON

PRÉSENTATION CLINIQUE DE LA MH JUVÉNILE.

Arq Neuropsychiatr 2006;64(1):5-9

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Objectif: Décrire les manifestations cliniques d'un groupe de patients ayant les premières attaques de la MH.

Méthode: Tous les patients ont été interviewés dans la structure d'un questionnaire clinique. On a déterminé leur génotype pour les répétitions CAG. Enfin, ils ont tous passé une IRM haute résolution.

Résultats: Nous avons identifié 4 patients ayant commencé la maladie juvénile, parmi 50 que nous suivons de façon prospective dans notre clinique neurogénétique. L'âge de départ varie de 3 à 13 ans; il y avait deux garçons, et 3 patients avaient un héritage paternel de la maladie. Les répétitions CAG variaient de 41 à 69.

Les plus jeunes patients montraient de la rigidité, bradykinésie, dystonie, dysarthrie, appréhension et ataxie. Les IRM ont montré de fortes pertes de volume des noyaux caudé et putamen ($p = 0,001$) et des réductions des volumes cérébral et cerebellum ($p = 0,001$).

Conclusion: 8% des patients Huntington de notre recherche clinique avaient la forme juvénile de la maladie. Il n'avaient pas les manifestations choréiques que les adultes présentent au départ. Il y avait une prédominance de rigidité et de bradykinésie. Deux autres points cliniques importants étaient l'appréhension et l'ataxie, que l'on peut relier à l'atrophie précoce corticale et à la perte de volume du cerebellum.

Clinical Characteristics of Childhood-Onset (Juvenile) Huntington Disease: Report of 12 Patients and Review of the Literature

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Whereas adult-onset Huntington disease is a well-characterized clinical entity, childhood-onset cases have not received as much attention. In this report, the clinical, demographic, and genetic characteristics in 12 patients with childhood-onset Huntington disease are presented and compared with data in the literature. The patients were divided into two groups based on age at onset of symptoms (≤ 10 or > 10 years old). The majority of patients had onset of symptoms before 10 years of age and most at or below 5 years of age. The delay in diagnosis was longer in those with earlier onset of symptoms. Inheritance was paternal in all patients with onset beyond 10 years of age. We found a preponderance of male patients in the younger age at onset group and of female patients in the older age at onset group.

The most frequent heralding symptom was cognitive decline in the group with earlier onset and oropharyngeal dysfunction in the later-onset group. Seizures occurred only in the younger age at onset group. Chorea was not a presenting sign but developed later in the course of the disease and, with dystonia, was more prevalent in the early age at onset group, whereas rigidity and bradykinesia were more prevalent in the older age at onset group. Patients in both groups developed gait, cognitive, and behavioral disorders at some point during the course of the disease. Furthermore, a slow and steady decline in IQ was observed on serial neuropsychologic testing in patients from both groups. Imaging studies were normal early and most commonly revealed neostriatal atrophy later in the course of the disease.

In this report, we describe the characteristics of 12 patients with childhood-onset Huntington disease and review those previously reported, expanding our knowledge about the features of childhood-onset Huntington disease, underlining the differences with patients with adult-onset Huntington disease, and suggesting a differential phenotype within patients with childhood-onset Huntington disease depending on the age at onset.

HD Lighthouse Contributing Editor's Comment:

Marsha L. Miller, Ph.D. Posted to the HDL: 25 Nov 2006

http://hdlighthouse.org/abouthd/juvenile/updates/1315jhd_characteristics.php

The authors review the case records of the twelve Juvenile Huntington's disease patients seen in their hospital's child neurology clinic from 1988 to 2002. CAG counts were available for five of the patients and ranged from 66 to 130. Eight patients had an affected father while four had an affected mother.

The age of onset ranged from 4 to 14 years. The earlier the age of onset, the longer it took to get a diagnosis, up to six years. Two patients were misdiagnosed with Attention Deficit/Hyperactive Disorder.

The symptoms differed between the group of patients who were below ten years of age at onset and those who were ten or older. The most common presenting symptoms in the younger group were cognitive problems such as declining school performance, regression in language skills, or an inability to learn to read. The most common presenting symptom in the older group was oropharyngeal dysfunction. (The oropharynx consists of the back third of the tongue, the soft palate, the tonsils, and the side and back walls of the throat.

Two of the five older patients also had cognitive problems at onset and two in the younger group had oropharyngeal dysfunction. Two in each group had fine motor problems, one in each had behavioral problems, and two of the younger group and one in the older had gait problems.

Ten out of the twelve patients developed oropharyngeal problems sometime during the course of the disease. Ten out of twelve developed upper motoneuron symptoms (increased reflexes, spasticity, Babinski sign). Four out of seven of the younger group developed seizures but none of the older group did. Although other studies associate dystonia (rigidity) with the earlier JHD onset and chorea with later JHD onset, this was not the case in this study. Chorea was not a presenting symptom for any of the children but developed in five of the seven earlier onset cases and in two of the five later onset cases. Dystonia was not a presenting symptom but developed in two of the seven earlier onset cases and one of the five later onset cases. IQ tests were performed repeatedly for four patients and all four showed decline over time.

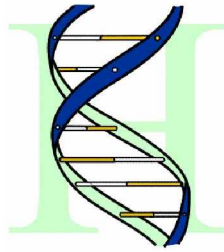
Ten of the patients had received EEGs. Eight were abnormal and two were normal. Some of the patients' brains appeared to be normal under imaging (PET or MRI) a year after onset but all showed abnormalities two years after onset.

Definitions: in a nutshell Oropharyngeal dysfunction is problems with swallowing and/or respiratory problems and motoneuron is the spasticity, spasms etc.

Oropharyngeal Dysfunction: Swallowing is a complex process involving a sequence of intricate timed maneuvers by a large number of muscles (including mouth, pharynx, larynx, esophagus, and diaphragm). Motor dysfunction is responsible for symptomatic illnesses both in the proximal skeletal muscle region and in the distal smooth muscle esophagus [oropharyngeal dysphagia]. Food aspiration is a frequent consequence of dysphagia, causing a strong risk of pneumonia and diet alterations. In some neurological diseases, dysphagia can persist for a long period, without being complained of by patients.

Upper motoneuron syndrome (UMN syndrome)

Spasticity is a disorder of the sensorimotor system characterized by a velocity-dependent increase in muscle tone with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex. It is one component of the upper motoneuron syndrome, along with released flexor reflexes, weakness, and loss of dexterity. The "negative" signs—weakness and loss of dexterity—invariably alter patient function when they occur. Symptoms are stiffness, contractures, atrophy and fibrosis.



MÉCANISMES PATHOGÈNES

DES FONCTIONS ET DYSFONCTIONS DE LA HUNTINGTINE AUX STRATÉGIES THÉRAPEUTIQUES

Celular and molecular Life Science.
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L'article est centré sur les fonctions cellulaires dans lesquelles la Huntingtine intervient et comment une meilleure compréhension des mécanismes pathogènes peuvent mener à une meilleure approche thérapeutique.

Bien que d'intenses recherches aient été menées dans les dernières années pour mieux comprendre la cascade moléculaire menant à la mort, plusieurs questions restent sans réponse. On ne comprend pas la spécificité de la mort neuronale dans le striatum, c'est à dire, pourquoi la huntingtine tue seulement les neurones du striatum. Des études ont identifié beaucoup de gènes qui augmentent ou diminuent sélectivement dans des neurones spécifiques pendant la maladie. Il devient nécessaire de faire une validation de ces gènes in vivo.

Parallèlement, un grand nombre de protéines interagissant avec la huntingtine ont été identifiées, mais on ne sait pas comment ces protéines interviennent dans le réseau en fonctionnement normal, ni comment le dérèglement de ces interactions affecte la physiologie de l'ensemble de l'organisme.

Dans la MH, le nombre de CAG est le facteur déterminant de l'âge de départ de la maladie. Néanmoins, il existe une variabilité significative de l'âge d'attaque de la maladie pour des individus qui ont le même nombre de répétitions CAG, ce qui suggère l'existence de facteurs modifiants. En effet, une étude extensive sur les populations vénézuéliennes ont montré que des facteurs génétiques contribuent de façon significative à cette variabilité. L'identification et la caractérisation de ces facteurs modifiants génétiques ou environnementaux est importante car leur modulation peut ralentir effectivement l'apparence des symptômes ou leur progression.

On a bon espoir que la validation de ces régulateurs importants de la toxicité de la huntingtine soit confirmée par une combinaison entre les études moléculaires dans les cellules et les modèles animaux d'après les études génétiques des patients MH.

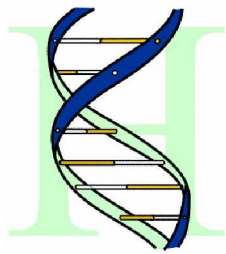
Une meilleure compréhension de la biologie de la huntingtine permet l'émergence de nouveaux concepts pour la maladie :

Premièrement, la MH ne devrait pas être considérée simplement comme une maladie de mort neuronale; (certes, des dysfonctions neuronales jouent un rôle important dans les manifestations et la progression des symptômes cliniques).

Deuxièmement, une augmentation de nouvelles fonctions toxiques de la protéine mutée et la perte des fonctions de protection de la huntingtine (wild-type) participent toutes deux aux mécanismes qui finalement mènent à la mort neuronale.

Etant donné l'importance de l'extension des polyQ mais aussi la fonction propre de la huntingtine et son influence sur la toxicité induite par les polyQ, des stratégies thérapeutiques devraient être orientées à la fois sur l'inhibition des dysfonctions neuronales et la mort, et aussi vers la restitution de fonctions normales à la huntingtine.

Note : Article complet (anglais) en ligne sur ce site (Fonctions et dysfonctions de la Huntingtine).



UN PEU DE VOCABULAIRE...

Source : Conférence IHA, Blankenberge sept 2006
Traitement de la maladie de Huntington
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Perturbations affectives (affective disturbances) : Relatif à l'humeur, la sensibilité, les attitudes.

Antipsychotique (antipsychotic) : Quasiment synonyme de neuroleptique.

Ataxie (ataxia) : Perte du plein contrôle des mouvements corporels.

Basal ganglia : Un ensemble de structures liées au thalamus dans la base du cerveau et impliqué dans la coordination des mouvements.

Bradykinésie (bradikinesia) : Du grec « brady » qui signifie « lent » et « kinesia » qui signifie « mouvement ».

Noyau caudé (caudate nucleus) : Un groupe de cellules nerveuses du basal ganglia dans le cerveau et qui jouent un rôle dans le mouvement et le comportement. Il est affecté chez les malades Huntington.

Inhibiteurs cholestérase (cholesterase inhibitors) : Médication qui augmente le niveau d'acétylcholine, composé qui est important pour la mémoire. Ces médicaments sont utilisés pour le traitement de la maladie d'Alzheimer.

Délusion : Une croyance ou une impression qui est maintenue fermement malgré la contradiction avec ce qui est généralement accepté comme une réalité ou un argument rationnel.

Dysarthrie (dysarthria) : Difficulté pour articuler clairement un discours qui par ailleurs est normal linguistiquement.

Dystonie (dystonia) : Un état de tonus musculaire anormal, donnant des spasmes musculaires et des postures anormales, typiquement due à une maladie neurologique ou à un effet secondaire de médicaments.

GABA : Gamma Amino Butyric Acid, un neurotransmetteur ou un agent de signal, important dans le basal ganglia.

Hypokinésie (hypokinesia) : du grec « hypo » qui veut dire « moins » et « kinesia » qui veut dire « mouvement ».

Neuropeptique (neuroleptic) : tend à réduire la tension nerveuse en diminuant les fonctions neurales.

Non-paternity : Le père n'est pas le père biologique.

Etude ouverte : (open-label study) : Une étude clinique dans laquelle le patient ainsi que le médecin connaissent le médicament qui est administré, par opposition à « double-aveugle ».

Parkinsonisme (parkinsonism) : autre terme pour les symptômes de la maladie de Parkinson, comme la lenteur du mouvement.

Placebo : Un médicament sans effets, procédure utilisée comme contrôle pour savoir si un médicament a seulement un effet psychologique bénéfique, ou une action physiologique réelle.

Prévalence : Nombre de patient dans une population donnée, à un instant donné.

Essai clinique randomisé en double-aveugle (randomized double blind clinical trial) :

Ni le patient ni le médecin ne savent si le patient a reçu le médicament testé ou un placebo.

Rigidité (rigidity) : Tonus musculaire augmenté, comme dans la maladie de Huntington ou de Parkinson.

Mouvements oculaires saccadés (saccadic eye movements) : Mouvements brusques des yeux, qui peuvent être volontaires ou réflexes, comme quand on est dans le train.

Sérotonine : un composé qui agit comme neurotransmetteur et a des fonctions importantes pour l'humeur et l'affection.

Striatum : raccourci pour corpus striatum, partie du basal ganglia et formé du noyau caudé et du putamen.

Thalamus : L'une des deux masses de substance grise située entre les hémisphères cérébraux de chaque côté du troisième ventricule, relayant l'information sensorielle et agissant comme un centre de perception de la souffrance.