Myotonic dystrophy:

A quantification of some clinical aspects of the classical form

J.P. ter Bruggen

MYOTONIC DYSTROPHY: A QUANTIFICATION OF SOME CLINICAL ASPECTS OF THE CLASSICAL FORM

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MYOTONIC DYSTROPHY: A QUANTIFICATION OF SOME CLINICAL ASPECTS OF THE CLASSICAL FORM

A clinical and neurophysiological investigation
(met een samenvatting in het Nederlands)

Een wetenschappelijke proeve op het gebied van de
Medische Wetenschappen

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This investigation was performed on the departments of neurology and ophthalmology of the St. Elisabeth and Maria Hospitals, Tilburg, the Netherlands; the IKNC of the University of Nijmegen, the Netherlands. Additional investigations took place on the departments of clinical neurophysiology of the St. Elisabeth Hospital, Tilburg, the Netherlands, FC Donders Institute of Ophthalmology, Utrecht, the Netherlands and Canisius Hospital, Nijmegen the Netherlands.

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Trefw myotonic atrophy\dystrophy

picture frontpage Statue of the Cyclads (2000 BC)

If one selfishly sees a thing
as if it were everything,
independent of the one and many,
then one is in the darkness of ignorance.

Anonymus, Bhagavad Gita ca. 1000 BC

Scientific work is investigating
throughout some minor aspects in detail,
which finally fit in a universal theory.

Stephen J. Gould, Wonderful Life 1989

aan Hanneke,
Floris-Jan en Feline

The main results from this thesis are reported in the following papers:

- ter Bruggen J.P., Bastiaensen L.A.K., Tijssen C.C., Gielen G.
  Disorders of eye movement in myotonic dystrophy.
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- ter Bruggen J.P., Tijssen C.C., Brunner H.G., van Oost B.A., Bastiaensen L.A.K.
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- ter Bruggen J.P., van Meel G.J., Paridaens A.D.A., van Norren D., Tijssen C.C.
  Foveal photopigment kinetics-abnormality: an early sign in myotonic dystrophy?
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- Verhagen W.I.M., ter Bruggen J.P., Huygen P.L.M.
  Oculomotor, auditory and vestibular responses in myotonic dystrophy.
  Arch Neurol 1992; 49: 954-960

- ter Bruggen J.P, Tijssen C.C.
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  Cognitive function in early adult and adult onset myotonic dystrophy with mild symptoms: neuropsychological and motor evidence (submitted).

CONTENTS

ABBREVIATIONS

BRS:	bulbar rating scale
CPP:	crystals in the cortex posterior
CTG:	cytosin-thymin-guanin
CAPK:	cAMP dependent protein-kinase
CMRO2:	cerebral metabolic rate of oxygen
CVLT:	Calnifornia Verbal Learning Test
DC:	dustlike crystals
EDS:	excessive daytime sleepiness
EL:	educational level
EMR:	eye movement registration
EOG:	electro-oculography
EOM:	extra-ocular muscles
ERP:	event related potentials
FWL:	focal white matter lesion
ICD:	inter commisural distance
IL:	iridescent lucencies
IWD:	interwave delay
LL-index:	liplength-index
LPS:	light peak substance
MDRS:	muscular disability rating scale
MRR:	maximum repetition rate
MSP:	maximum sound prolongation
MT-PK gene:	myotonin protein kinase gene mutated in MyD
MyD:	myotonic dystrophy
OH:	ocular hypotonia
OKN:	optokinetic nystagmus
PCC:	polychromatic crystals
PTA:	pure tone audiogram
RPE:	retinal pigment epithelium
SI or S-index:	snout-index
SP:	smooth pursuit
ST:	swallowing test
SWCT:	Stroop Word Colour Test
TMT:	Trailmaking Test
VFT:	Verbal Fluency Test
Vmax:	maximum velocity of the visually guided saccades
VOR:	vestibulo-ocular-reflex
WAIS:	Wechsler Adult Intelligence Scale
WCST:	Wisconsin Card Sorting Test

INTRODUCTION

Myotonic dystrophy (MyD) has been recognized as a disease entity for approximately a century. In the same year Batten and Gibb (1909) and Steinert (1909) independently reported a series of patients with progressive muscular atrophy and weakness of facial and distal limb muscles, who were unable to relax the hand muscles after a forceful contraction (myotonia). During the following decennia, the involvement of multiple organ-systems was defined: cardiac conduction defects, smooth muscle involvement, hypersomnia, reduced intelligence and a lack of initiative in the early onset cases. These were accompanied by cataracts, abnormal glucose response, increased anaesthetic risk and in males, typical premature baldness and testicular atrophy (Harper, 1989). Since 1992, a diagnostic accuracy nearing 100% can be reached by a combination of clinical examination and DNA techniques (Reardon et al., 1992; Mahadevan et al., 1992; Brunner, thesis, 1993; Wieringa, 1994). At present, despite significant effort, there remains no treatment that will alter the natural history of muscular dystrophy (Harper, 1989).

The early contributions by Fleischer (1918) and Vogt (1921) described in detail the inheritance pattern, using the typical multi-coloured cataract as a marker for MyD. Fleischer (1918) suggested that MyD is a hereditary illness, the severity of which depends on the age of onset and increases in successive generations. The disease may be transmitted for many generations without obvious symptoms, with the possible exception of cataract. This peculiar autosomal dominant inheritance pattern was confirmed by others in several other countries (Thomasen, 1948; Bell, 1947; Klein, 1958; Höweler, 1986, 1989). In Bell's review (1947), most studies revealed a remarkable trait: the disease presented earlier with increasing severity in subsequent generations (anticipation). This assumption was ignored by Penrose (1948) but confirmed by Klein (1985) and finally led to a reluctant acceptance of the anticipation theory by Höweler and associates, as shown in their work (1986, 1989).

Three main clinical forms of MyD were recognized by Dyken (1969) and Dyken and Harper (1973): a 'congenital' adult and late onset form. This clinical classification was expanded by Höweler (1986) and more recently by Koch (1991), who divided their adult onset cases into two subgroups, these are, early adult and late adult (see Table 1). The late onset form of MyD is characterized by a very mild symptomatology: cataract is commonly the only feature, but in some cases a mild facial weakness and myotonia may be present. The 'congenital' form is the most severe, with at birth severe hypotonia, insufficient respiration and impaired swallowing (Harper, 1975; Hageman, 1993). Some of the cases may have talipes or arthrogryposis. Those surviving the neonatal period show mild to moderate mental retardation and later, develop the same pattern of muscular weakness as the adult onset form. This form, also termed the classical form of MyD has its onset in adolescence or in early or later adulthood. The majority of patients show the classical trait

Table 1a. Clinical division of MyD in subgroups

type	onset	initial symptoms	late symptoms	CTG*
childhood MyD	congenital	neonatal diffuse hypotonic paresis, respiratory insufficiency, clumbfeet. Maternal inheretance. Incomplete recovery.	mental retardation. After 10 yrs of age progressive weakness, cataract, GI motility disorders.	> 600
	1–12 yrs	mental retardation, neonatal symptoms absent.	multi-organ signs	
adult onset or classical form MyD	12–50 yrs	myotonia with typical weakness: face, pharynx, distal limbs.	slow prog. weakness, finally proximal. Wheelchair: 5%, mental slowness, apathy, hypersomnolence.	about 100 to about 1300
	12–20 yrs	as well testis-atrophy, infertility, sometimes social isolation.	variable organ involvement: cataract, conduction cor, complications by partus and anaesthesia.	
late onset or mild MyD	> 50 yrs	cataract	myotonia, mild muscle-dystrophy.	50 to about 100

adapted from Höweler et al., 1986; Koch et al., 1991; Harley et al., 1993

*: approximation of CTG repeat-length

of myotonia, muscle weakness and in later stages cataract, in combination with some other organ-specific signs.

After the discovery of the genetic abnormality in 1992 it became clear that the distinct clinical subtypes must have a genetic basis. Simultaneously, Aslanides et al. (1992), Brook et al. (1992), Buxton et al. (1992), Fu et al. (1992), Harley et al., (1992), Jansen et al. (1992) published the discovery of the genetic abnormality. They showed that a polymorphic CTG repeat (Cytosin-Thymidin-Guanin) in the 3′ untranslated region, located at the q13.3 band of chromosome 19 was the major defect.

While the normal gene has between 5 and 30 CTG repeats, the MyD alleles vary from 50 to several thousands (Brunner et al., 1992; Harley et al., 1993). Using DNA techniques, the aforementioned clinical subgroups, depending on age of onset, are broadly correlated with the CTG repeat expansion (Harley et al., 1993; see Table 1).

The clinical expression of MyD is variable, even within the same family, although the disease is genetically homogenous (Harper, 1989). The latter author stated that clinical variability in fact is a hallmark of MyD. It is true that the variability correlates with the size of the repeat expansion. Some incomplete correlation between genotype and phenotype can be defined: an

earlier onset and a greater severity broadly correlates with a longer CTG repeat (Hunter et al., 1992; Tsilfidis et al., 1992, Harley et al., 1993). The strongest correlation was apparent between CTG repeat length and muscle involvement and to a lesser degree with heart and brain (Pizzuti et al., 1993 a.o.). However, the correlation is neither linear nor absolute. For instance, some infants who are severely affected with congenital MyD have small expansions (Tsilfidis et al., 1992). Patients with MyD occasionally show a marked somatic mosaicism of the CTG repeat length (Ashizawa et al., 1993; Anvret et al., 1993; Thornton et al., 1994; Janssen et al. 1994). In one investigation skeletal muscle DNA from 8 adult patients with the mild to moderate type of MyD showed a repeat of more than 1500, while in 5 of them, the repeat size was substantially shorter in leucocytes DNA (Ashizawa et al., 1993). Moreover, in sperm the (CTG)n repeat excess was often longer in adult cases than the repeat in leucocytes in the same patient (Janssen et al., 1994).

At the time of preparing this document, the effects of the gene products on the separate organ systems remain uncertain (Ptacek et al., 1993; Wieringa, 1994). Because the gene product is a myotonin-proteinkinase, one may expect an influence on the phosphorylation processes (Fu et al., 1992) in the several membranes, with consequences for the ion transport and finally intracellular damage (Griggs et al., 1990; Benders et al., 1993 a.o.).

AIM AND OUTLINE OF THE STUDY

Recent investigations have demonstrated that MyD patients differ from one another not only in clinical features but also regarding genetic defects. In addition, the length of the (CTG)n excess broadly correlates with the four clinical types. A review of the literature demonstrated that most of the previous investigations usually included all the various clinical subtypes. Therefore, it appears that clinical studies should be performed for selected groups of MyD patients.

The leading questions of this thesis were as follows:

1. What is the additional diagnostic value of sensitive quantitative measurements?
2. What is the pattern of early expression in some organ systems?
3. How does the spectrum of organ-system involvement clinically present itself in an adult onset group of MyD patients?

Based on clusters of clinical features, several authors divided the MyD population into 4 or 5 clinical subgroups (Dyken, 1969; Dyken and Harper, 1973; Höweler, 1986; Koch, 1991). In this series of clinical studies we confined ourselves to the adult onset group only.

Prior to the detection of the gene defect, our goal was to give particular attention to increasing diagnostic accuracy by special quantitative clinical investigation methods. At a later stage, when adequate genetic markers became available, the focus of our studies shifted to early expression related clinical issues in an adult onset group of MyD patients of mild severity.

Aim and design of the studies

As far as possible, a choice was made to confine the study to the *adult onset or classical form,* this being the most numerous (> 50%) group. Only *common* MyD related signs were included. In the later studies we focused on a rather early phase of the disease. Another choice, was to use *quantitative methods,* which reflect the course of the slow progressive nature of the illness in a more efficient manner. For practical reasons the above mentioned method was chosen to study some unknown aspects of common organ involvement in MyD. Thus, we performed studies concerning neuro-ophthalmology, neuro-otology, bulbar weakness, speech and neuro-psychology.

A selective review of the literature, limited to these selected topics, will be given in chapter 1.

In chapter 2, the results of the study of eye movement disorders, retinopathy and opticopathy, mainly for an adult onset group are described with regards to pattern, pathophysiological mechanism, expression mode and course.

In chapter 3, the findings of several neuro-otologic investigations for an adult onset group are presented.

In chapter 4.1, an easy bedside method to detect the swallowing abnormalities for an adult onset group is documented.

In chapter 4.2, the results of a computerized speech analysis in a mildly affected adult onset group are documented.

In chapter 5, the neuro-psychological pattern is presented for a mildly affected adult onset group.

CHAPTER 1

SELECTIVE REVIEW OF LITERATURE

1. MYOTONIC DYSTROPHY

1.1. Neuro-ophthalmology

1.1.1. Historical perspective

The early studies of several ophthalmologists were major contributions to the knowledge of myotonic dystrophy (MyD). Although it is impossible to discuss them all, a short historical review will be given. Greenfield (1911) was the first to stress the importance of cataracts as a feature of MyD. It was Fleisher (1918) who noted the relationship of clinical symptology and the age of onset and outlined the crude lines of the inheritance pattern, including anticipation (the severity of the disease increases during successive generations). Furthermore, a part of his contribution was a description of the second phase of development of cataracts. Shortly after the discovery of the slitlamp in 1920, lens inclusions were recognized as a characteristic of MyD after the publication of Vogt (1921), who also reported the chronological sequence of development of these (multicoloured) cataracts. The first person to perform a large scale population study was Klein (1958), who gathered the largest family study to date in Switzerland. With regards to The Netherlands, Vos's (1938) thesis, entitled 'cataracta myotonica' should be mentioned. 'Because this dissertation was written in Dutch it did not receive the international publicity it deserved', wrote the Dutch ophthalmologist Junge (1966). The thesis of the latter 'ocular changes in dystrophia myotonia, paramyotonia and myotonia congenita' carefully documents the different ophthalmologic abnormalities for the period up to 1967 in MyD, which comprises amongst other topics detailed descriptions of cataracts, retinopathy and histology. In the same year Burian and Burns (1967) reported in an excellent article regarding the eye in MyD. The remaining literature up until 1989 has been summarized by Harper in his monography about MyD. Recently, Ashizawa et al. (1992) described the diagnostic value of separate ophthalmological findings in a group of patients in whom accuracy of the diagnosis was confirmed for the first time by haplotype-analysis.

In the following paragraphs, the literature regarding neuro-ophthalmological topics in MyD will be summarized.

1.1.2. Lens opacities

Vogt (1921, 1931) documented the successive phases of lens inclusion in MyD. The following features were listed by Vogt (1931) as characteristic of MyD: white opacities interspersed with coloured opacities, a sufficient number of such opacities and no opacities in the anterior or posterior zones of discontinuity.

There are 4 stages of development (Table 2). The first or Vogt stage is characterized by a bi-lateral appearance of dust-like irregular shaped white opacities intermingled with iridescent crystals of varying red and green (less frequently yellow and blue) immediately beneath the anterior and posterior

Table 2. Slitlamp findings in MyD

phase 1	no visual symptoms; some dust-like white and multi-coloured opacities in the anterior and posterior cortex. Pos. predictive value or: **PPV: 100%***.
phase 2	usually no visual symptoms; the opacities increase in density along the lens sutures (star shaped). **PPV: 100%***
phase 3	diminution of visual acuity; subcapsular vacuoles and waterclefts occur, lenticular sclerosis exacerbates while coloured opacities become less suspicious. **PPV: uncertain.**
phase 4	impaired vision; mature cataract. **PPV: 0%.**

Vogt, 1921, 1931
*Ashizawa et al., 1992

capsules of the lens-cortex. Visual symptoms are usually absent. In the second or Fleisher stage (1918), the opacities become more diffuse, they increase after years in density and develop a stellate shape.

This may sometimes result in slightly reduced vision. In the third and final stage water clefts, vacuoles and lamellar separations develop, resulting in complete opacity with definite impaired vision. The fourth phase of mature cataract cannot usually be recognized as myotonic cataract since the multi-coloured crystals have disappeared (Vogt, 1921, 1931; Junge, 1966; Duke Elder, 1969).

The differential diagnosis for iridescent lucencies (IRL, previously: multicoloured crystals) is rather diverse. Sporadic IRL may occur in several diseases: hypothyroid disease, hypocalcaemia, juvenile diabetic mellitus, mongoloid idiocy, autosomal dominant cataract, idiopathic IRL (especially in young females) and due to the effects of various drugs (neuroleptic drugs, silver and gold-compounds) (Junge, 1966; Roy, 1989).

Electronmicroscopy of lenses with cataracts removed from patients with MyD revealed a number of unusual features such as lipid droplets, vacuoles containing whorled material and protein crystalloid deposits (Dark and Streeten, 1977). The most remarkable finding is that the IRL are probably whorls of plasma membranes and no real crystals (Eshagian et al., 1978).

Regarding the prevalence and age related occurrence of lens opacities, Klein (1958) in his population study, found lens opacities in 237 of the 242 patients (97.9%). The youngest patient with definite myotonic cataract was reported by Klein (1958) being 10 years of age, although sporadic and non-specific lens opacities can be found at a younger age (Harper, 1972, 1973). Cataracts may be the only manifestation of the disease in about 5–10% of the MyD population (Bundey and Carter, 1970; Polgar et al., 1972) and in late onset, form lens opacities may be the sole manifestation for many years (Harley et al., 1993).

Höweler (1986) separated the occurrence of the typical myotonic cataract (IRL) into several age groups: 0% < 10 yrs, 46% 10–29 yrs, 67% 30–49 yrs and 87% above 50 yrs of age. Similar results were discovered by others (Klein, 1958; Junge, 1966 and Harper, 1989). Therefore the typical myotonic cataract

probably does not occur below 10 years of age and the frequency of lens opacities increases with age. No certain data is available regarding the speed of progression, simply because no longitudinal investigations have been reported to date.

How is the frequency of occurrence of cataract in the several sub-groups, dependant upon the age of onset? In the childhood group 4/16 (25%) showed myotonic cataract (only after the first decade of the disease), in the early adult onset group 22/50 (44%), in the late adult onset group 11/15 (73%) and in the senile onset group all 21 (100%) patients (Höweler, 1989). Cataracts are for the congenital group extremely rare, but may occur in the later stages (Harper, 1972).

What are the practical uses and misuses of slitlamp investigation for genetic research? Polgar (1972) studied the value of lens-inclusions and EMG for 'early detection'. It was concluded that EMG and slitlamp studies were useful methods to discover some clinically asymptomatic gene carriers in family studies. The question of how many asymptomatic first degree relatives were affected was answered by Harper (1973), who found 17.6% of them definitely affected and 13.7% suspicious but not diagnostic. Although Harper (1973) suggested that nearly all heterozygotes may be detected by the age of 14 years, Bundey et al. (1970, 1974) demonstrated that this statement might be true, but not before 40 years of age. Finally, Brunner (1991) demonstrated for a group of DNA proven MyD patients, that approximately 8% of the patients remained undiagnosed, regardless of neurological investigation, EMG and slitlamp-investigation. The same author (1991) stated that in particular, aspecific unilateral or sporadic IRL are often false positive and induce unnecessary DNA studies. Using the guidelines of Ashizawa (see further), this number can certainly be reduced. The use of DNA markers as a golden standard, enabled Ashizawa (1992) to solve some long standing uncertainties regarding lens-inclusions and define the sensitivity and specificity of the other lens-opacities other than IRL.

For a group of definite MyD gene carriers, Ashizawa (1992) discovered in 18/30 patients IRL, bilaterally in 14/18 and in the remaining 4 patients unilaterally. The number of IRL was less than 10 in 13/28 eyes, 10 or more in 9 eyes and disregarded in 6 eyes of the 14 MyD patients with bilateral IRL. Ashizawa compared these findings with a group of 'non-MyD patients'. None of the 49 'non-MyD patients' showed bilateral IRL but four of them exhibited unilateral IRL, totalling 4 IRL. Ashizawa suggested some rules to increase the specificity of slitlamp investigation for MyD. Firstly, a population of MyD must be taken which raises the apriori change 10.000 times compared with the normal population. Other recommendations are: lens inclusions should be investigated by an ophthalmologist experienced in identifying more subtle lens opacities of MyD, using a stationary slitlamp, and only if IRL are found bilaterally and outnumbering 10 (?) per eye, can they be regarded as pathognomonic (Ashizawa et al., 1992). Furthermore, one may include the posterior cortical cataract (PCC), but firstly it must be distinguished on

morphological grounds from the other types of co-existing posterior cortical and posterior subcortical capsular opacities (age-related, steroid-related and congenital). Ashizawa and allies (1992) also warned about excluding the diagnosis of MyD merely based on slitlamp findings (neg. predictive value of 92% for combining IRL and PCC (Ashizawa et al., 1992). Genetic counselling with regard to lens-opacities for 'asymptomatic' gene-carriers has shown that it is quite reliable (true-positive results in 18/20 patients) (Longstaff et al., 1991). Harley found that for asymptomatic groups with a CTG repeat of less than 100 the lens inclusions may occur as sole manifestation (Harley et al., 1993).

1.1.3. Retinopathy

Since the reports of Verwey and Le Gras (1933) and Gotfredsen (1949) macular degeneration and tapetoretinal degeneration are recognized as features of MyD.

In the initial phase, the retinopathy is clinically undetectable or may give atypical blurred vision with sometimes moderately (20–35 deg.) bilateral constricted visual fields (Burian and Burns, 1967). In such cases, the retinopathy was diagnosed based on fundoscopy or electrophysiological tests in population studies (Table 3). For criteria concerning retinopathy see the separate textbooks (e.g. Walsh and Hoyt, fourth edition). Colour vision is normal and night blindness is absent, but the dark-adaptation threshold is usually diminished (Table 3). In the series of Junge (1966) and Burian and Burns (1967) the majority of patients had a visual acuity above 0.6. Sometimes the visual acuity is severely reduced, due to maculopathy, cataract or a combination of both.

It is difficult to gain a clear picture of the retinopathy as seen by ophthalmoscope. The findings are variable with some findings being included by chance due to a sample error in the small series (N=15–52) and lens opacities sometimes obscure the retinal abnormalities. Most reported abnormalities are located in the peripheral retina (12–53%) (Burian and Burns, 1967; Junge, 1966; Hayasaka et al., 1984). According to the latter these lesions are presumably at the level of the deep retinal layer and do not substantially alter the visual functions. The major abnormality in the retinal periphery are the gross clumpy pigmentations (Burian and Burns, 1967; Junge, 1966), sometimes in combination with rather unique yellow peripheral flecks (20%) (Hayasaka et al., 1984). In up to 20% of the patients the retina is diffusely involved so that a so called butterfly dystrophy or a reticular dystrophy may be observed (Deutman, 1974; Hayasaka et al., 1984). In the macular region, a minority of patients (4–20%) have aspecific streak-like or pigmented macular lesions (Burian and Burns, 1967; Junge, 1966; Meyer et al., 1980). Some authors also suggest a dysfunction of the photoreceptors (Junge, 1966; Burians and Burns, 1967). Another remarkable finding was the narrowing of the retinal arterioles in relatively young patients (Burian and Burns, 1967).

Most evidence for a retinopathy comes from the electrophysiological studies.

About 60–83% of the electrophysiological retinal studies were bilaterally grossly abnormal regardless of ocular symptoms or the appearance of visible fundus abnormalities (Junge, 1966; Kirkham and Coupland, 1981; Sandrini et al, 1986; Pinto et al., 1987; Kerty and Ganes, 1989). A common but aspecific finding was the bilateral reduction of b-wave amplitude in the ERG, both in scotopic and photopic conditions, with rarely a prolonged implicit time factor, (Burian and Burns, 1966; Stanescu and Wawernia, 1970; Stanescu and Michels, 1975). Although the ERG abnormalities are partly influenced by the under exposing of the retina by cataracts, the rods in the retina seem diffusely involved in MyD. Pinto et al. (1987) recorded pattern-ERG's which were either absent or of low amplitude indicating a bipolar-ganglion cell layer dysfunction. The same author also found subnormal electro-oculography (EOG) indices using the dark trough method, indicating that the pigment epithelium must be somehow involved. EOG changes (36%) are probably less frequent than ERG changes (83%) in electrophysiological tests (Junge, 1966). To summarize, one may assume a pathological process that invariably affects both the retina (pigment-epithelium, bipolar-ganglion cell layer and rods in the peripheral retina), the photoreceptors and macula.

Relevant histo-pathological studies are usually autopsy studies and do not exceed 3 patients each, (Manschot et al., 1968; Burns, 1969; Houber and Babel, 1970; Betten 1971; Ginsberg, et al. 1978; Meyer et al., 1980), except the study of Sarks et al. (N=5) (1985). The reported findings are too variable and insufficient to give a consistent pattern of retinopathy. The common main changes are disorganization of the peripheral retina: scattered drusen, colloid deposits within a slightly thickened Bruch's membrane (Ginsberg et al., 1978) and cystic changes (Betten, 1971). In addition, diffuse variable atrophy of all retinal layers, pigment *increase and hypertrophic pigment epithelium* (Manschot, 1968; Houber and Babel, 1970; Meyer et al., 1980) and variable loss of

Table 3. *Retinopathy and opticopathy in Myotonic Dystrophy*

Abnormal.in.	Junge N = 52	Burian-Burns N = 25	Pinto N = 14	Hayasaka N = 15
Concentric vis. fields	2/52	7/22	10/14	0/6
Dark adaptation	31/36	24/24	np	0/6
Fundoscopy				
– macula	3/52	6/14	?	2/8
– retina	6/52	4/12	?	8/15
ERG				
– photopic	30/86#	?	9/14	0/8
– scotopic	71/86#	low b-2	3/14	1/8
EOG	28/78#	np	6/14	0/8
pVER	np	np	11/12	np

#: eyes
np: not performed

photoreceptors were reported (Betten et al., 1971; Houber and Babel, 1970, Sarks et al., 1985). Perhaps this is specific for MyD when taking into account that *hypertrophy* of the pigment epithelium is peculiar for most other tapetoretinal *degenerations* (Houber and Babel, 1970). The study of Sarks et al. (1985) is the only study reporting EM findings of the retina. The main finding was an accumulation in the macular region of lipofucsin in large hyperpigmented cells in all 5 investigated MyD patients.

The relationship to age or group, depending on the age of onset, is to be questioned. Only one longitudinal study has been reported, indicating that the retinopathy is progressive (Yoshihiro et al. 1993). The youngest patient described with retinopathy was 10 years of age (Burian and Burns, 1967), while in larger series nearly all investigated individuals with MyD showed abnormal results. This opinion is shared by Harper (1989), who mentioned ERG as a potential screening test. No correlation however can be found with age. To date no data exists for the retinal dysfunction in the separate age onset groups.

1.1.4. Optical nerve neuropathy and the visual cortex

Six early studies reported pallor of the discs by fundoscopy in MyD (Ortleb, 1912; Hauptmann, 1918; Heine, 1925; Lohlein, 1914; Franchetti, 1963; Junge, 1966). Junge (1966) concluded that clinical evidence for an optic neuropathy was exceptional (3/52). Furthermore, other signs suggesting an optical nerve neuropathy were negative. The visual fields were within the normal range, without central scotoma. Colour vision is usually normal, except for supersensitive tests like 100Hue, which are more related to retinal connections than optical dysfunction (Babel, 1981). In addition, the subclinical or sluggish pupil reactions may probably indicate a sphincter pupillae dysfunction rather than an optic nerve lesion (Thompson,1964; Spaide et al.,1984; den Heyer et al.,1991). Therefore, clear clinical evidence of an optical nerve dysfunction or a lesion anywhere else in the visual pathways is lacking (Harper, 1989).

Visual evoked potential studies (VEP), which are considered to be near field potentials of the visual cortex (Celesia, 1982, 1985), repeatedly revealed abnormalities.

In approximately 60–92%, VEP recording in MyD showed a symmetrical prolongation of P100-latency or a decrease of amplitude, both of flash VEP (Kirkham et al., 1981) and pattern reversal VEP (Gott et al., 1983; Pinto et al., 1987; Kerty and Ganes, 1989). This finding alone is aspecific, but suggests a disturbance of axones and myelin in the visual pathways.

The VEP findings may indicate a bilateral prechiasmal abnormality of the visual pathways of unknown exact localization (Gott et al., 1983), but others suggested an abnormal functioning of the visual cortex (Kerty and Ganes, 1989). An abnormality of the visual cortex is unlikely because no other arguments can be listed (Harper, 1989) and MRI studies show a normal morphology of the visual cortex (Damian et al., 1992). Junge (1966) suggested that optical nerve involvement might be interpreted as secondary atrophy of the optic nerves as a consequence of primary retinal degeneration. To date, no

certain relationship between ERG and VEP has been reported, except in one study by Sandrini (1986), who reported an inverse relationship of VEP latency and ERG b-wave amplitude.

Pinto (1987) tried to clarify the question of prechiasmal or postchiasmal retinal dysfunction. He studied simultaneous recordings of pattern-ERG (pERG) and pattern reversal VEP (pVEP) and also found evidence of a dysfunction of the postretinal pathways (Pinto et al., 1987).

Pathological abnormalities of optical nerves or visual cortex are not reported separately to be abnormal (Coers, 1952; Berthold, 1958; Bethlem, 1958; Refsum 1966; Harper, 1989), except in cases with mental retardation, in which the gyral architecture may show minor abnormalities (Rosman and Kakulas, 1966).

Is optical neuropathy related to age or the age of onset? VEP alterations may occur in mildly affected MyD patients (Gott et al., 1983). The youngest patient with a definite abnormal VEP was 27 years of age (Gott et al., 1983), whilst in some series (Kerty and Ganes, 1989) the percentage of abnormalities shows a trend towards an increase with age. The course of VEP changes are unknown. No specific studies for the age of onset groups are reported prior to the compilation of this document (1994).

1.1.5. Low intraocular pressure

Although in 1932 Granstrom had already suggested that ocular hypotonia (OH) may occur in MyD, the studies of Junge (1966) and Burian and Burns (1967) made it clear that the intraocular pressure is consistently low with minimal diurnal fluctuation. The latter authors found intraocular hypotension in nearly all investigated (N=51 and 23) patients (84–100%). Junge (1966) found mean values approximating 8.8 mmHg (SD: 3) with a range of 2–15 mmHg. Burian and Burns (1967) reported a mean ocular pressure of 10 mmHg (SD: 9). However, the broad overlap with the normal population (mean: 15.5, SD 2.5; 99% interval 10.5–21 mmHg) (Goldmann and Schmidt, 1958) appeared to limit the value of OH (pressure below 11 mmHg) as a sensitive sign for (early) diagnosis.

Degeneration of the ciliary muscle in association with reduced aquaous secretion in the ciliary epithelium seems to be the likeliest cause for this phenomenon (Walker et al., 1982; Blanksma et al., 1983).

In 1992 Ashizawa published the results of OH in asymptomatic gene carriers, mildly affected MyD patients (N=32) and 51 controls. An intra-ocular pressure of 11 mmHg or less was found in 35 eyes of 19 patients and 5 eyes of 3 'non-MyD patients'. In his study, OH was a rather indefinite (0.59) but highly specific (0.94) sign for MyD.

What is the relationship between age and specific subgroups? The youngest patient reported with OH, was 11 years of age (Junge, 1966). Although data of longitudinal studies are lacking, the course seems progressive as may be concluded from the positive relation with age (Burian and Burns, 1967). Unfortunately Junge (1966) could not confirm this relationship. The course

itself is unknown. Particular studies for the separate age dependent subgroups have not been performed to date.

1.1.6. Extra-ocular muscle dysfunction

Patients with MyD seldom complain about diplopia and clinical neuro-ophthalmological investigations rarely reveal abnormalities of eye movements except some degree of ptosis. Clinical studies (Burian and Burns, 1967; Dyken, 1967; Ashizawa et al., 1992) mentioned some restriction of gaze in up to 50% of patients. Lessell et al. (1971) mentioned a single patient with external ophthalmoplegia. Nowadays the eye movements can be investigated more precisely by electro-oculography (EOG) or infra-red or magnetic coil studies. Extra-ocular myotonia was seldom noticed in EMG studies of the extra-ocular muscles (Davidson, 1961; Zauberman, 1969).

Decreased maximum velocity of small and large amplitude saccades has been reported in a limited (N=3–10) series of patients (von Noorden, 1964; Baloh et al., 1975; Oohira et al., 1985), sometimes more pronounced for horizontal than for vertical eye movement (Emre and Henn, 1985). Other oculomotor changes include hypometric saccades and disturbances of smooth pursuit (von Noorden, 1964; Bollen et al., 1990, 1992).

Electro-oculographic studies of eye movements in MyD have so far yielded conflicting interpretations as to the underlying pathophysiological mechanism. Some authors have suggested a central origin for the eye movement disorders (von Noorden, 1964; Burian and Burns, 1967; Lessell et al., 1971; Bollen et al., 1991, 1992), while others have considered that they are caused by a more peripheral mechanism (Junge, 1966; Oohira et al., 1985).

The extra-ocular muscles are histologically quite distinct from limb muscles. A small number of light-microscopic studies have been reported each involving less than 8 patients (de Jong, 1955; Bethlem, 1955; Davidson, 1961; Pendefunda et al., 1964; Junge, 1966; Houber and Babel, 1970; Ketelsen et al., 1972). The common pattern was slightly atrophic muscle fibres, a mild diffuse increase in connective tissue and a diffuse increase in nuclei in the sarcolemma. The nuclei were seldom arranged in rows. One electron-microscopic study (Kuwabara and Lessell, 1976) revealed aspecific alterations similar to the changes of the peripheral muscles (Harper, 1989). Hoogenraad performed enzyme histochemical studies on one MyD patient. He found no abnormal results (Hoogenraad et al., 1979, 1982). Although the content of ragged red fibres is high in extra-ocular muscles, one author reported an excess of 20% (Isashiki et al., 1989). A reduced cytochrome-c-oxidase activity in both extra-ocular muscles as well as skeletal muscles in 0.4–20% was found using enzyme histochemical techniques (Isahishi et al., 1989; Ono et al., 1986; Yamamoto et al., 1989).

No relationship between eye movement disorders and age, duration of the disease or neuromuscular deficit, has been reported so far. The studies are too small and heterogenic to appoint the youngest patient with a certain oculomotor dysfunction. One may expect an early onset, based on frequent

strabismus found in children with MyD (Harper, 1989). No studies are confined to the age of onset related subgroups.

1.1.7. Peri-ocular muscle dysfunction

Bilateral ptosis is already recognized as a characteristic aspect of MyD and this was first published by Steinert (1909) and Batten and Gibb (1909). Its frequency is high (> 60%) (Burian and Burns, 1967; Harper, 1989; Ashizawa et al., 1992). The weakness of the vulnerably thin levator palpebrae muscle lies in the morphological substrate (de Jong, 1955). Even in infants, this sign may be positive and therefore is regarded as an 'early sign' (Junge, 1966). As to be expected, even in minimally affected patients, some degree of ptosis is present (Mathieu et al., 1992; Ashizawa et al., 1992). The course of ptosis is definitely progressive (Harper, 1989) and positively related to age. The ptosis can be corrected by lid elevating spectacles or surgical treatment.

Weakness of the orbicular ocular muscles sometimes accompanied by myotonia, appears more frequently (Steinert, 1909; Ashizawa et al., 1992). The consequences of atrophy of the orbicularis oculi muscles include lagophthalmos, ectropion, eversion of the puncta lacrimalis, blepharoconjunctivitis and epiphora (Junge, 1966). Likewise, peri-ocular myotonia is early in onset, and has a low sensitivity (0.03) and high specificity (1.0) (Ashizawa, 1992). When testing weakness of the orbicularis oculi muscles in gene carriers and mildly affected patients manually, the same author found somewhat different numbers: sensitivity 0.61 and specificity 0.98. The course is definitely progressive, correlating with age (Harper, 1989). To date, no studies with regards to the peri-orbicular muscles and specific age dependent subgroups have been presented.

1.1.8. Miscellaneous (other ophthalmological signs)

Stern (1978) reported in 9/18 MyD patients focal and generalized abnormalities of the *iris vascular pattern* on fluorescence angiography. *Corneal lesions* like keratoconjunctivitis sicca or corneal ulcers were described by Burian and Burns (1967) in 8/25 cases and by Junge (1966) in 6/52 patients. Furthermore, *enophthalmus* (18–50%) (Klein, 1958; Junge, 1966) may occur in MyD. The 18% of Junge is more probably due to the fact that he used an objective measurement criterion (< 10.2 mm, Hertel value). Remaining ocular phenomena were *lagophthalmus* (2/52, Junge, 1966), *ectropion* (1/52, Junge, 1952) and frequent *excessive lacrimation*, which is perhaps a secondary phenomenon (Junge, 1966).

1.2. Neuro-otologic system

Impairment of hearing is not a conspicuous complaint in patients with MyD and is not largely appreciated (Harper, 1989). In 1966, Kuhn and Eye first reported hearing loss with definite audiogram abnormalities as a frequent sign in affected adults. The frequency of hearing loss is approximately 25–35% (Kuhn and Eye, 1966; Wright et al., 1988). Usually the audiogram reveals a progressive loss in high and medium frequency hearing both in children (O'Brien and Harper, 1984) and in adults (Wright et al., 1988). The study of Wright et al. (1988), is the most complete, demonstrating that in 17 out of 25 adults, a mostly bilateral (13/17) sensorineural (14/17) hearing loss, was profound in ten cases. The absence of complaints in patients was remarkable, indicating a gradual onset. Wright (1988) also performed brain auditive evoked potentials (BAEP) studies and MRI studies of the 8th nerve. BAEP results were abnormal in 3 out of 5 cases, (two were normal, two displayed severe peripheral hearing loss and the last one showed bilateral delayed peak V latency). MRI failed to reveal any acoustic nerve abnormalities. Wright states that in particular adult MyD patients have a much greater chance of developing a serious hearing loss. Unfortunately no correlations to the onset and severity of muscular symptoms were reported. In the same study tympanic membrane mobility was also found to be reduced in about 30% of the patients (Wright et al., 1988).

Two explanations can be given for hearing loss in MyD. In the congenital group Harper and O'Brien (1984) discovered hearing loss in 10 out of 46 patients as a consequence of otitis media. The high frequency of otitis media in childhood cases is probably causally related to the presence of weakness of the facial and palatal muscles and secondary bony deformation of the skull (O'Brien and Harper, 1984). Secondly a dysfunction of the cochlea or cochlear nerve – not visualized on MRI –, as a result of the underlying membrane dysfunction in MyD, is likely in the adult onset group (Kuhn and Ey, 1966; Wright, 1988).

Vertigo is an exceptional symptom in MyD and probably unrelated to processes causing hearing loss. BAEP abnormalities are common (30–53%) (Thompson, 1983; Ragazzoni et al., 1991), also indicating that the auditory pathways must be frequently involved. The BAEP findings are heterogenic with variable peak I, III and V latencies and sometimes show prolonged central conduction, represented by prolongation of III-V interpeak latencies. Functional abnormalities in the central acoustic pathways have been reported in small studies of adult cases. This may be concluded both from BAEP results (Zakrisson and Blom, 1982, Yamane and Nomura, 1984; Thompson, 1983; Zeithofer et al., 1986; Wright et al., 1988; Ragazzoni et al., 1991) and from delayed stapedius relaxation (Kuhn, 1966). In addition, the acoustic processing of (long latency) BAEP is also deranged (Perini et al., 1989; Ragazzoni et al., 1991).

When summarizing, one may assume that sensorineural hearing loss appears to be caused simultaneously on a peripheral and central level, although rarely giving rise to symptoms.

Morphological studies (Bethlem, 1958; Harper, 1989), pay no specific attention to changes of the acoustic/vestibular apparatus. Brainstem morphological studies did not reveal abnormalities (Coers, 1952; Berthold, 1958; Rosman and Kalukas, 1966, Refsum, 1966).

Except in the studies of O'Brien (1984) – concerning congenital onset patients – and Wright (1987) – concerning adult onset patients, no other correlations are known with regards to the relationship to the age of onset or age dependent subgroups.

1.3. Peri-oral and bulbar weakness

1.3.1. Peri-oral muscles

Facial weakness (levator palpebrae, orbicularis oculi and mimic muscles in cheeks, chin and perioral region) has been recognized as a common feature since the earliest descriptions of MyD (Batten and Gibb, 1909; Steinert, 1909).

In earlier stages of the disease, myotonic symptoms predominantly in the facial muscles, may cause eyelid spasm, stiffness or slowness of the tongue and jaw muscles (dysphagia, dysarthria) (Harper, 1989). More frequently, subclinical facial myotonia verified by EMG occurs (Polgar et al., 1972, Bundy et al., 1972, 1974; Streib et al., 1987; Mettler et al., 1990). The distribution of facial myotonia was studied by EMG by Streib (1983). In particular, he found myotonic discharges in the orbicularis oris (95% abnormal results found in 25 MyD patients) but less frequently in the masseter muscles (52%) or sterno-cleisomastoids (50%). Myotonia correlated positively (R=0.62) with the severity of muscle weakness (Streib et al., 1983). At a later stage a progressive weakness and atrophy of facial muscles occurs. To illustrate this, Harper (1989) presented four successive pictures of the same patient at the ages of 17, 30, 44 and 56 years. The pattern of facial muscle weakness in MyD is characteristic, imparting a peculiar appearance of the individuals affected. Terms such as 'facies myopathica', 'hatched face', 'lugubrious', and 'hollowed out' have all been used to describe the facial appearance in MyD.

In the initial stage of the adult type disease, the facial abnormalities are mild and not as marked as in facio-scapulo-humeral (FSH) dystrophy or in neurogenic facial palsies. In the congenital form (Harper, 1989), facial weakness is more pronounced and as a result of the weakness and mal-development of the jaws and a triangular deformation of the mouth or 'shark' mouth is nearly pathognomonic.

Quantitative assessments of facial function have rarely been reported. Only Pryse Philips et al. (1982) clinometrically studied the rest position of the facial muscles, including the perioral, using photographs.

Morphological investigation of the perioral muscles revealed similar chronic myopathic abnormalities as did the limb muscles (Thomasen, 1948).

The rather typical myopathic facies with gaping expression can be recognized from early adulthood onwards (Steinert, 1909; Thomasen, 1948). A positive relationship with age must be presumed, although longitudinal studies fail (Harper, 1989). No studies involving peri-oral muscles in the age of onset dependent subgroups are reported.

1.3.2. Swallowing

Upper gastro-intestinal motility disturbances are most common and cause considerable morbidity in MyD (Chiu et al.,1962). Swallowing difficulties are almost a constant feature of MyD (prevalence: 60–80%) (Harper, 1989). In general, dysphagia is more pronounced in solids than in liquids (Horowitz et al.,1987b). It is peculiar why major swallowing abnormalities occur whilst there is a complete absence of complaints (Swick et al.,1981; Horowitz et al.,1987b). Whilst in moderate phases, dysphagia may already be present (Bosma and Brodie, 1969), in many cases, a life threatening aspiration is the first presentation of the swallowing disorder.

Barium-contrast and manometry studies showed evidence of a variable weakness of oesophageal contractions and diminished upper oesophageal sphincter pressure, with normal sphincter relaxation (Swick et al., 1981; Eckhart et al., 1986; Siciliano et al., 1990). In addition, stomach emptying is delayed (Horowitz,1987b) and small intestine motility is reduced (Nowak et al., 1984). Harper (1989) considered retention of food in the pharynx and pooling in the vallicula as the most constant finding. Motility of gastric emptying can be ameliorated by drugs (Horowitz et al., 1987 a,b).

In moderate phases, it is probably myotonia and in more severe phases oesophageal weakness that are mainly responsible for dysphagia (Bosma and Brodie, 1969). One quantitative assessment of swallowing has been reported using a videofluoroscopy (VDF) Barium technique (Johnson and McKenzie, 1993). These authors recorded in 12 MyD patients (aged 16–36 years) the kinematic pharyngeal transit times. The results of VDF do not completely reflect the severity of the swallowing problem in MyD patients, especially in MyD patients with a longer disease duration (more than 15 years). In 4 patients, the VDF underestimated for unknown reasons the swallowing disorder.

Morphology is not essentially different from the limb muscles (Pruzanski et al., 1967; Nowak et al., 1982). As regards dysphagia, the striated muscles in the upper one third of the oesophagus are more involved in the disease process than the smooth muscles (Eckhart et al, 1986).

The relationship of swallowing with age, limb muscle weakness or the age of onset dependent subgroups is uncertain. No clear relationship has ever been reported with age. From adulthood onwards, dysphagia may occur (Pettengell, 1985). The course is assumed to be progressive but longitudinal studies have not been reported. The lack of correlation between subjective and

objective dysphagia makes historical comparisons unreliable (Swick et al, 1981). The assessments of severity of dysphagia seem unrelated to the severity of limb muscle weakness (Horowitz et al, 1987a). No selective studies have been reported which were restricted to the age of onset groups.

Thus, sudden aspiration or postoperative aspiration remains an unpredictable and serious complication during the course of the disease, which may even occur in moderately affected patients (Bosma and Brodie, 1969).

1.3.3. Speech

The speech disorder present in the majority of patients is rather specific. Steinert (1909) and Batten and Gibb (1909) were the first to notice a speech abnormality in MyD. Thomasen (1948) described it as follows: 'the speech disorder is characteristic; in almost all cases it is very rapid, not to say gabbling; the voice is monotonous, sometimes hoarse, weak and nasal'.

The sporadic studies regarding speech in MyD are anecdotal, small, qualitative and usually lack control groups (Nonne, 1905; Siemerling, 1905; Batten and Gibb, 1909; Steinert, 1909; Thomasen, 1948; Rouques, 1931; Thomasen, 1948; Caughy and Myranthopoulos, 1963; Maniecka, 1969; Calvet et al., 1970). As a consequence of the facio-bulbar weakness, these studies commonly report a pattern of flaccid dysarthria. No circumscript speech dysfunction can be derived from these reports. In any case, from the literature it is unclear which physiological mechanisms are underlying. Also the clinical descriptions do not assess a concomitant disorder of speech programming (apraxia of speech).

Only two studies are quantitative, showing some phonatory instability. Calvet (1970) reported quantitative findings about the voices of 2 MyD patients. He requested that the patients produce a sustained vowel /a/. The only abnormal finding was a 'higher voice fundamental frequency' (the number of vocal folds vibratory cycles per second) in both patients. Ramig's (1988) quantitative study is the most extensive. He studied 6 patients with MyD. Their voices were recorded on tape and analyzed. This author also studied the 'maximum sound prolongation' (MSP) of the vowels /a/, /i/ and /u/. The major quantitative result was that the MyD patients had a cycle to cycle variation ('jitter'), three times greater in the period of the acoustic output pressure during MSP than controls.

Ramig suggested that the myopathic or myotonic changes of the laryngeal muscles are responsible for these periodic variations of speech. The correlations between speech and bulbar muscle-groups or a possible coexistent dyspraxia of speech remain to be established.

Dystrophic morphological changes in the pharynx, larynx, velum palatinum are reported which do not essentially differ from the chronic myopathic changes in the limb muscles (Albrecht, 1920; Thomasen, 1948). Morphological investigations of the brainstem did not reveal any major abnormalities (see chapter on neuro-otology) and the primary speech areas are usually spared on MRI (Huber et al., 1989; Damian et al, 1992).

Up to the time of this writing (1994), no certain correlation between speech and age has been demonstrated. From early adulthood onwards, a nasal or slurred speech may occur (Steinert, 1909; Maniecka, 1969; Ramig, 1980). Although longitudinal studies are lacking, most authors agree that the flaccid dysarthric speech becomes progressively worse (Thomasen, 1948; Myrantho-poulos and Caughy, 1963; Harper, 1989). To our knowledge specific studies dividing the population into age of onset subgroups have not been performed.

1.6. Mental impairment

1.6.1. Historical perspective

Abnormalities in the intellectual functions in adults with MyD have been recognized since the early publications regarding MyD (Bramwell and Addis, 1913; Adie and Greenfield, 1923; Maas and Paterson, 1937). High percentages (35–65%) of intellectual dysfunction were noted in large survey studies (Thomasen, 1948; de Jong, 1955; Klein, 1955; Höweler, 1986). In his study of 101 cases, Thomasen (1948) found 36% of his population had a 'considerable degree' of intellectual involvement, 41% were 'somewhat' impaired and only 24% were considered to be clinically normal.

It is difficult to define this mental impairment in clinical terms. Additionally, in the majority of the early clinical studies regarding cerebral involvement, intellectual, personality and psychiatric symptoms, these were intermingled. Caughy (1963) reviewed the changes in mental state and described, in agreement with Thomasen (1948), three different types: more or less pronounced intellectual deterioration, considerably reduced initiative and a carefree temperament. In his series, fatigue and adynamia are prominent symptoms. Daytime somnolence is often present and gives the impression of apathy. Furthermore social deterioration is a feature in families afflicted by this disorder (Thomasen, 1948). In spite of the physical and mental disability, patients exhibit a carefree temperament as illustrated by Maas and Paterson (1937): 'they are generally satisfied and cheerful and do not easily get angry.' This point of view has been shared by many others, including Harper (1979, 1989).

In order to clarify the spectrum of intellectual dysfunction several standardized neuro-psychological studies have been performed since 1980 (see further on). Apart from the great variability of methods and results, most studies had visuo-spatial and visuo-constructive dysfunction in common. Unfortunately, to date, no close matching with the clinical type has been reached but in general the earlier the onset, the more severe the neuro-psychological abnormality (Thomasen, 1948; Dyken and Harper, 1973). In recent years, correlative studies with advanced imaging methods (MRI, SPECT, PET) have been performed. So far neuro-psychological studies in relation to genetically defined patients groups have not been performed.

1.6.2. Clinical description

The clinical presentation of intellectual involvement is quite variable and is difficult to interpret. Thomasen's (1948) description is perhaps most accurate but concerned the picture of a full blown mental impairment: 'the reduced initiative is often misinterpreted as laziness and disinterest; they are easily overcome by sleep and the reduced initiative is parallel with intellectual deterioration; a remarkable indolence, carelessness and contentness which glaringly contrasted with the physical incapacity; they think they manage excellently which causes conflicts with healthy family members'. This description however, rather outlines a patient with longstanding disease than the average patient.

Caughey's impression (1963) may illustrate this attitude: 'While in the country in search of a certain "myotonic" home, it was often possible to identify a residence by its neglected appearance, the obvious need of repairs, the unkempt yard and garden choked with overgrown grass and weeds, which provided a vivid contrast with the surrounding well-kept homes'.

1.6.3. Neuro-psychological studies

A number of neuro-psychological studies have been performed in order to define a certain pattern of the cognitive impairment. Another question, is, what is the relationship between a functional alteration and the reported cerebral abnormalities? A selection of the most important reports will be discussed in chronological order highlighting the main aspects. Details can be found in Table 4.

Dyken and Harper (1973) split up their population of MyD patients and found a difference in IQ between the separate groups depending upon the age of onset. In total 29 MyD patients were investigated, among whom 19 patients with congenital MyD (mean full scale IQ: 71), 10 patients with the adult onset type (mean IQ: 100) and 8 unaffected parents (mean IQ: 107).

Woodward et al. (1982) studied the neuro-psychological features of 17 MyD patients choosen at random, who were attending a neuromuscular clinic and compared the results with 25 controls. They found moderate overall intellectual impairment in the patient group with a mean full scale IQ of 95 and none in the retarded range. The mean IQ of the control group was significantly higher: 112. No correlation could be found between mental impairment and severity of muscular symptoms.

Bird et al. (1983) included 29 patients and studied the cognitive and personality functions in MyD. The mean full scale IQ was 90 and 6 individuals were in the retarded range. All the MyD patients were grouped together and a control group was missing. The weakest cognitive abilities were immediate recall, abstraction, spatial manipulation and orientation. Overall, 32% of the patients had prominent personality disturbances; a figure that is not excessively high in a population with such physical, social and mental problems.

Portwood et al. (1986) performed a pilot study with 43 MyD patients in order to solve the relationship between cognitive dysfunction and maternal or parental inheritance. The mean full scale IQ was 87 for the MyD population. At least 3 patients had to be classified as retarded and no control group had been used. Psychological results were similar to the previous studies. The most important finding, was that there is, no significant difference in mental performance for maternal or paternal inheritance pattern.

Stuss et al. (1987) gathered 19 MyD patients (12 with early onset and 7 with late onset) from the Childrens Hospital with a mean full scale IQ of 87 and compared the results with a same number of controls matched for IQ and education. Among the patients 2 were retarded. The leading question was whether MyD could be listed as a subcortical 'dementia'.

Firstly, I would like to expatiate on subcortical dementia. This is characterized by a marked psychosocial incompetence associated with minimal memory loss and as a rule, absence of aphasia, apraxia or agnosia. Characteristic symptoms include forgetfulness, slowing of the thought processes, mild intellectual impairment, apathy, inertia, depression and the inability to manipulate knowledge. Difficulties in problem solving and abnormalities of judgement and insight may occur (Cummings et al., 1984; Dunne, 1993).

Neuro-psychologically, the patients of Stuss performed at a low average level. Visual perceptual and visual constructive abilities were impaired. Stuss stressed that age of onset was related to poor test performance. No arguments could be supplied by Stuss et al. to presume a subcortical 'dementia'.

Huber et al. (1989) examined 41 MyD patients using neuro-psychological procedures and MRI. The mean full scale IQ was 87 for both patients and 16 controls. No differentiation was made between clinical subtypes. Ten patients had severe intellectual impairment. Problems with calculation (mini mental state examination), fluency, digit-span and visuo-spatial functions were the most pronounced. Depression was more frequent in the patient group. No relationship could be found between intellectual functions and neuromuscular deficit or sex. Furthermore, there was a correlation between maternal inheritance and a more severe intellectual dysfunction. Huber confirmed the findings of Stuss (1987) showing a relationship between an earlier onset and a more severe mental impairment. On MRI, focal white matter lesions and temporal lobe abnormalities were significantly more common in patients with severely disturbed intellect.

Pernini et al (1989) performed a controlled study with 27 patients (mean full scale IQ: 87), amongst whom, 4 were in the retarded range. Their aim was to detect a relationship between cognitive dysfunction and electrophysiological measures. In approximately 50% of the patients, a significant global impairment of cognitive functioning was found. The event-related auditory evoked potentials, (50% low and 50% absent P300-amplitude, whilst latency was normal), correlated with the intellectual impairment.

Censori et al. (1990) studied the general neuro-psychological profile in MyD. They included 20 MyD patients and 20 age and education matched controls

Table 4. *Review of literature neuropsychological functions in myotonic dystrophy*

author	N	age	IQ	Ed.	MR	M.	P	contr	onset	Stroop	TMT	Flu	WCST	Mem.	Visc	D.
1. Bird #	29	36	90	?	0 3	9	17	–	?	–	–	–	–	a	a	Y
2. Brumback #	18	16	86	?	0.6	?	?	–	+	–	n	–	–	n	n	Y*
3 Broughton#	8	37	95	12	?	?	?	–	?	a^	n	–	–	n	n	–
4. Censori #	20	39	?	7	0.5	9	7	+	?	–	–	n	n	n	a	–
5 Franzese @	28	37	105	9	0.07	9	7	–	+	–	–	–	–	n/a	n/a	Y*
6. Huber #*	41	38	87	13	0.4	8	22	+	+	–	–	a	–	a	a	Y
7. Lohman #	41	36	98	?	0.4?	5	25	+	+	n?	–	–	a	n	a	–
8. Malloy #*	20	40	85	11	0.3	?	?	+	?	–	–	–	n	a	a	–
9. Perini #	27	39	87	?	0.8	8	15	+	?	–	–	–	–	–	–	–
10. Portwood #	43	36	?	?	?	10	18	–	?	–	–	–	–	a	a	–
11. Stuss #*	19	35	87	11	0.4	?	?	+	+	a^	n	n	–	n	a	N
12 Woodward #*	17	37	95	12	0 2	?	?	+	?	–	a	a	a	a	a	–
13. Walker #	22	39	96	?	?	?	?	+	?	–	–	–	–	n	a	N
14. Chang #	23	37	87	12	?	8	14	+	+	–	–	–	–	a/n	a	–

*: exclusion criteria for other organic mental diseases
#. more than one subgroup of MyD
@· adult onset group
N number of MyD patients
age: mean age of MyD patients
IQ· mean (preverbal and verbal) IQ
Ed.: years of education
MR: percentage of IQ<80
M.: maternal inheretance, the remainders inheritance is unknown
P : paternal inheritance
contr. age/sex/ education matched control group
onset: percentage of congenital and early adult onset

D.: depression:
Y: yes. tested
Y*: yes: tested, correlation mental disorder
N· no: tested but no correlation
TMT: Trailmaking (visuospatial)
Flu.: Fluency (frontal lobe)
WCST. Wisconsin Card Sorting Test (frontal lobe)
Mem : several memory tests
Visc.: other visuospatial and constructional abilities
Stroop: test for attention
a: abnormal result
n: normal result
a^: abnormal result compared with healthy controls

in their study. IQ was not reported separately. No division into subtypes was accomplished. This study is complete and claims to outline a general pattern. In general, intellectual function has globally decreased and most test results have scores in the lower quadrant of normal. The cognitive dysfunction pattern found in this study is suggestive of a 'right hemisphere impairment': visuo-spatial and constructional disabilities prevail (up to 50%), often associated with 'frontal lobe' dysfunction (verbal fluency/Wisconsin Cart Sorting Test), compounded by alterations in memory and language in the more severe cases.

Malloy et al. (1990) investigated the course of the disease in 20 MyD patients (mean full scale IQ: 85; mean age: 40 years) and compared the results with age and IQ matched controls. No clinical subgroups were studied. This group of authors concluded that the motor deficits may progress but the cognitive deficits are mainly developmental and rather stable.

Franzese et al. (1991) performed an uncontrolled study with 28 MyD patients (mean full scale IQ: 105). This study alone, included the age of onset as a selection criterium. In all cases, the disease began in early adulthood or in adult life and the disease duration varied significantly from 2–40 years. The average profile showed a marked deficit on digit span subtest and milder deficits in arythmic, picture arrangement and block design. Only 7% of the patients showed low intelligence with deterioration of the perceptual-motor functions.

Chang et al (1993) studied the cerebral abnormalities in MyD. In a controlled study (N=22), they performed psychological tests and cerebral bloodflow studies (quantitative MRI, 133-Xenon and SPECT). The mean full scale IQ's of the (early) adult onset MyD patients was 87 (SD: 18). Both visual perception and visual construction were significantly different from age-matched controls. A reduced cerebral perfusion was most severe in the frontal and temporo-parietal association cortex and correlated with IQ and perhaps with earlier onset.

Summerizing these neuro-psychological studies, some conclusions can be drawn. The IQ of the MyD patients in most studies was below average (IQ= 100) and the IQ of maternally inherited disease was lower than that of paternally inherited disease. In most studies a differentiation for the age of onset was not made. The cognitive impairment is highly variable and probably differs per age of onset group: most severe in the congenital and early adult onset group and lacking in the mild (or senile) group of MyD. As the mental impairment may be progressive as is the muscular disorder, it is remarkable that the duration of the disease has been mentioned separately. This may also account for the wide range of IQ's (87–110) found. As most prominent cognitive impairment, inability to perform visuo-spatial and visuo-constructive tasks has been reported (Table 4). A purer pattern of mental impairment might have been outlined if clinically, more homogenous groups would have been studied and if a uniform method of testing would have been used. In

addition, the question remains unresolved as to whether non-retarded patients already have any mild cognitive deficit(s) at the onset of the disease.

1.6.4. Additional cerebral investigations

Nowadays, most authors consider functional and structural cerebral abnormalities as a variable and disease-related feature of MyD (Harper, 1989).

1.6.4.1. Neuro-physiological studies of the central nervous system in MyD. Diffuse abnormal neuronal function may be derived from the results of EEG and event related potential-studies. EEG recordings showed an excess of theta and delta wave activity and sharp focal wave discharges (Barwick et al., 1965; Op de Coul and Kortbeek, 1967; Lundervold, 1969). Small studies (6–27 patients), with regards to the auditory event related potentials (ERP) showed either absence or delay of peak N2 and P3, despite a correct tone-discrimination (Raggazoni et al., 1991). Nevertheless, the amplitude of P3 was sometimes reduced or absent (Perini et al., 1989). These abnormalities in auditive ERP's indicate global mental impairment (Perini et al., 1989).

Anecdotal evidence can be gathered for a functional abnormality of the brainstem. However, the BAEP and SSEP findings, the missing late response (R-2) of the blink-reflex in the majority of MyD patients, supported such an assumption (Messina et al., 1976).

1.6.4.2. Neuro-radiological evidence for central nervous system involvement. Some authors found dilatation of the (cerebral) ventricles as an explanation for the mental decline. Serial pneumo-encephalographic findings were indicative of a progressive diffuse cortical atrophy (Refsum, 1961, 1967) but were not accompanied by specific neuro-psychological data. Walker (1984) and Avrahmi (1987) confirmed the dilatation of the ventricles and cerebral atrophy on **CT studies**. However, Walker et al. (1984) were unable to reproduce the findings of Refsum (1967) when it became clear that ventricular size did not correlate either to age or mental impairment. To summarize, a progressive hydrocephalus is unlikely to cause the mental changes.

Cerebral **MRI** showed abnormalities of up to 70% in cases of MyD. Most of these abnormalities are aspecific except global atrophy, ventriculomegaly, periventricular hyperintensity and focal white matter lesions. These bilateral non-specific focal white matter lesions can be characterized as high signal lesions in the anterior-medial temporal region (Glantz et al., 1988; Huber et al, 1989) or fronto-(temporo)-parietal regions (Damian et al., 1993), with similar symptoms as in demyelinating disorders (Huber et al., 1989). The most important reports regarding MRI abnormalities will be outlined in the following paragraphs.

Huber et al. (1989) compared the neuro-psychological and MRI findings in a population of 41 MyD patients (mean full scale IQ: 87, mean age 38 year, 24% retarded). This group demonstrated that the MRI findings (focal white matter lesions, global atrophy and temporal lobe lesions) correlated to the

severity of mental dysfunction. In particular, the FWL's showed a significant correlation to the severity of a crude rating for intellectual status. Magnetic resonance findings in this study indicated that, while the focal cerebral atrophy was not related to severity of intellectual impairment, skull thickness, focal white matter degeneration and temporal lobe abnormalities were significantly more common in MyD patients with severely disturbed intellect.

Damian et al. (1992) performed a transversal MRI-study on cerebral white matter lesions and crude neuro-psychological ratings. The authors studied 25 patients (IQ unknown, mean age 36 years, of whom 20% were retarded) with a disease duration of 0–24 years. MRI findings indicated cerebral atrophy in the majority (81% of whom 36% were severe) and bilateral large focal white matter lesions (68%) in the fronto-(temporo)-parietal regions. Even excluding patients with mental retardation, intellectual impairment correlated to cerebral atrophy and focal white matter lesions. Furthermore, the occurrence of focal white matter lesions were more commonly seen in early onset cases with maternal inheritance. A remarkable finding was that 9 out of 11 patients with a duration of at least 10 years, showed multiple focal white matter lesions, whilst in the group with a duration of less than 10 years, only in 2 out of 10 patients could such focal white matter lesions be demonstrated. An earlier onset and longer disease duration thus appears to be related with increasing number and volume of focal white matter lesions. The MRI findings provide an argument for slow progression of the cerebral alterations in MyD.

In contrast, Chang et al. (1993) performed neuro-psychological tests and quantitative MRI investigations in 22 childhood and adult onset cases of MyD (full scale IQ: 87, mean age of 37 years, mean duration of disease 14 years and an unknown percentage of retarded patients). Except for small bright T2-signal areas in the regions of the inferior and medial temporal cortex, no FWL's were reported. These changes were interpreted as volume averaging effects of the adjacent cisternal spaces secondary to mild atrophy in the temporal lobes.

Chang et al. (1993) studied the same group of 22 MyD patients, using **133-Xenon**. The patients with MyD, had significantly lower regional cerebral bloodflow (rCBF) (mean 38.9 +/− 7.6 ml/100 g per minute) than controls (mean 50.9 +/− 3.3 ml/100g per minute). The lowest values (33.2 +/− 6.5 ml/100g per minute) were found in the temporal regions and to a lesser extent in the frontal regions.

Single Photon Emission Computerized Tomography **(SPECT)**, using 99mTc HMPAO, was also studied by Chang et al. (1993). The HMPAO uptake was abnormal in all 22 early adult and adult onset MyD patients. In twelve of them, a bilateral hypo-perfusion was found temporo-parietally. Sixteen patients showed a decreased uptake in the fronto-temporal regions. The patients with maternal inheritance (or early adult onset) showed a global hypo-perfusion and those with paternal inheritance (or adult onset), a more temporo-parietal and frontal hypo-perfusion.

Fluoro-deoxy glucose (FDG) **PET** scan studies gave a somewhat different, but not contradictory view.

Fiorelli et al. (1992) studied the cerebral glucose utilization in 11 adult MyD patients (IQ unknown, mean age of 35 years). Concomitant brain diseases were ruled out by MRI, with MRI only showing minimal to moderate cortical atrophy. The FDG-PET scan results showed a 20% decrease of cortical glucose utilization and a reduction of glucose delivery to the brain. In addition, there was a large overlap between the metabolic rate of patients and controls. Due to the fact that neuro-psychological studies were omitted in that investigation, a link between cognitive dysfunction and PET scan data is absent. Notabally, some clinically symptom-free gene carriers had the highest metabolic rate of the entire group. A diffuse cortical glucose metabolism cannot rule out a subcortical origin.

Mielke et al. (1993) studied the cognitive functions and FDG-PET scan in 3 mentally impaired MyD patients. Two patients (age 42 and 50 years), had their onset in childhood and one in adulthood (age 59 years). All patients fulfilled the criteria of DSM-III for organic psychosyndrome but without evidence for 'dementia'. Mielke and allies found on FDG PET, not only a diffuse cortical and subcortical dysfunction but also a preferential decrease in both frontal regions and lentiform nuclei.

Summarizing the neuro-radiological studies several conclusions may be drawn. The localized MRI findings are variable but related to cognitive impairment. In particular, the bilateral fronto-(temporo)-parietal and anterior medial temporal focal white matter lesions appear to be unique for MyD and to correlate to the severity of mental impairment (Huber et al., 1989). Furthermore, the focal white matter lesions correlate to disease duration, indicating a progressive course (Damian et al., 1992). Other evidence for a frontal and subcortical abnormality is supplied by the FDG-PET scan study of Mielke et al. (1993). The 99mTc HMPAO SPECT- and 133-Xenon studies (Chang et al., 1993) correspond rather well with the (fronto) parieto-temporal lesions on MRI. Taken together, most neuro-radiological studies appear to indicate the existence of widespread and variable bilateral lesions in the fronto-parieto-temporal regions.

1.6.5. Sleep disturbances

In MyD, excessive daytime sleepiness (EDS) is a common sign (Thomasen, 1948; Harper, 1989), despite a sleep duration of sometimes more than 10 hours a night (Harper, 1989). The quality of sleep may be reduced due to nocturnal hypoventilation. The latter is thought to be caused by a combination of a weakness induced obstructive (Broughton et al., 1990) and a central sleep apnoea syndrome (van Hilten et al., 1993; van der Meché et al., in press). For a relation between sleep and cognitive dysfunction see chapter 1.6.9.

Two recent reports with regards to sleep will be described more extensively.

Hilten et al. (1993) studied 10 patients with EDS. The main finding was a prolonged mean cycle duration and decreased stability of NREM/REM cycle.

These findings suggest that EDS in MyD, reflects a complex and widespread malfunction of the circadian and ultradian timing system.

Van der Meché et al. (in press) studied 22 MyD patients. Seventeen of them complained about EDS, resembling 'ideopathic hypersomnolence'. A sleep apnoea syndrome may have contributed to only 3 out of 17 patients. Therefore, the authors suggested that EDS is due to a dysfunction in central sleep regulation and not disturbed nocturnal breathing.

Thus, the hypersomnolence during the day must be regarded as a predominant dysfunction of the central sleep regulation with unknown localization (van Hilten et al., 1993; van der Meché et al., in press). The positive effects of Ritalin on vigilance, support the assumption of such a central component (van der Meché, 1986). It is speculative to localize the disturbance of central sleep regulation in MyD in the thalamic regions (van Hilten et al., 1993). Two reports support this hypothesis. First, Lugaresi (1986) described a fatal familial insomnia syndrome (Lugaresi et al., 1986) with primarily, involvement of anterior and dorsomedial thalamic nuclei; peculiarly, in the same thalamic areas in MyD, inclusion bodies were found by Culebras et al. (1973).

1.6.6. Morphological studies of the central nervous system

Older morphological studies did not reveal major cerebral abnormalities or have provided little detail on microscopy of the brain (Coers, 1952; Berthold, 1958; Refsum, 1966). However, Rosman and Kalukas et al. (1966) found in all 3 (congenital) mentally retarded patients, of whom, one had alveolar hypoventilation, reduced weight of the brain, minimal changes in the gyral architecture and disordered cellular arrangement in the subcortical white matter.

Culebras et al. (1973) and Wisniewski et al. (1975) reported, in 6 patients, an excess of eosinophilic inclusion bodies in 10–30% of the thalamic neurons which can also be found in less than 1% of non-diseased elderly brains. Other studies confirmed these findings (Pena et al., 1980; Ono et al., 1987). Ono (1987) also reported inclusions outside the thalamus, localized in the cerebral cortex, caudate nucleus and putamen.

Neuro-fibrillairy changes, similar to those as in Alzheimer's disease, have been reported all over the brain in MyD, in particular in the parahippocampal region and remaining (para)limbic system (Sarai et al., 1969; Mitake et al., 1987; Kuroda et al., 1988; Yoshimura et al., 1990; Kiuchi et al., 1991). The most important of these studies will be discussed.

Massive neurofibrillary changes in the parahippocampus and several structures of the limbic system and basal forebrain nuclei were reported in two siblings by Kuroda (1988).

Yoshimura et al. (1990) studied the topographical distribution of neurofibrillary changes in a 61 year old adult onset patient with obvious mental impairment and a disease duration of more than 30 years. He found bilateral involvement of the parahippocampus, hippocampus, amigdaloid nucleus, fusiform gyrus, insula, olfactory bulb and many changes in the nucleus basalis of Meynert, inferior temporal gyrus, hypothalamus and brain stem and a few

changes in the cingulate, frontal and temporal gyri, neostriatum and mammillary bodies Yoshimura's study (1990) stated that the significance of thalamic inclusions in previous studies (see above) was overestimated

1 6 7 Relation to the duration of disease

A mental impairment may be the first symptom of MyD (Howeler, 1986, Harper, 1989) in a minority of patients The controlled transversal study of Malloy (1990) suggested a rather stable cognitive dysfunction, related to age, but not progressive, in contrast with the clinical impression Contrastingly, the transversal study of Damian (1992) provides evidence of progression in confluent bilateral white matter lesions corresponding with disease duration Only one clinical longitudinal study (Bird et al , 1983) has been reported which mentioned no decline in mental function after a follow up of 11 and 19 years in five individuals with MyD

1 6 8 Relation to the age of onset

Howeler (1986) confirmed the findings of Dyken and Harper (1973), that the severity of the mental disorder correlates to the age of onset groups Howeler found mental alterations in all the congenital cases studied, in half of the early onset group but not in the senile onset or mild group These findings are in agreement with other previous studies (Thomasen, 1948, Harper, 1975) Maternal inheritance was also related to a more severe mental retardation, probably because all congenital onset patients have maternally transmitted disease (Harper, 1989, Huber, 1989) For the adult onset form this is uncertain (Franzese et al , 1991)

Another author who studied a circumscribed adult onset group is Franzese (1991) He found an intellectual dysfunction in only 7% which in particular, consists of an abnormality in the 'digit span' subset of the WAIS, besides a disturbance of spatial functions and calculation

Yoshimura (1990) studied the morphological alteration in a single 61 year old adult onset patient with a disease duration of more than 30 years He found clinical evidence for intellectual impairment and found an excess of Alzheimers's neurofibrillary changes scattered in the brain (see chapter 1 6 6)

1 6 9 Relation to sleep disturbances

It is known that patients with respiratory disturbances may exhibit global neuro-psychological deficits (Greenberg et al , 1987) In MyD, excessive daytime sleepiness (EDS) is a common sign (see chapter 1 6 5)

Broughton (1990) studied the relation of neuro-psychological deficits and sleep disorder There was no correlation in this study between cognitive deficit and degree of sleep fragmentation Both the neuro-psychological deficit and the EDS probably represent CNS lesions independent from one another

In conclusion, the relationship of psychological dysfunction and cerebral abnormalities remains obscure The cluster of neuro-psychological dysfunction

as described by Censori et al. (1990) suggests a 'right-hemisphere' dysfunction but the bilateral MRI, SPECT and PET scan findings are contradictory, with regards to lateralization and localization. Despite no unequivocal neuropsychological arguments can be given for a subcortical dementia, the lack of initiative and carelessness is reminiscent of a diffuse subcortical involvement. The latter is compatible with the bilateral widespread involvement of the (para)limbic system (see 1.6.6). The excessive daytime sleepiness is additional evidence of a widespread subcortical central nervous system lesion, that superimposes the mental impairment. By studying further homogenous groups (depending on age of onset, maternal or paternal inheritance and severity) this discrepancy might be elucidated.

CHAPTER 2.1

DISORDERS OF EYE MOVEMENT IN MYOTONIC DYSTROPHY

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(Brain 1990; 113: 463–473)

INTRODUCTION

Myotonic dystrophy (MyD) is an autosomal dominant multisystem disorder with variable penetrance, in which dystrophic changes, apart from the predominant muscle involvement, are also evident in the central and peripheral nervous system (Jamal et al., 1986). Patients with MyD seldom complain of diplopia and clinical neuro-opthalmological investigation rarely reveals any disturbance of eye movement except for some ptosis. Electro-oculographic (EOG) studies on disorders of eye movement in MyD have so far yielded conflicting interpretations as to the underlying pathophysiological mechanisms. Decreased maximum velocity of small and large amplitude saccades has been reported in limited series of patients (Baloh et al., 1975; Oohira et al., 1985), sometimes more pronounced for horizontal than vertical eye movements (Emre and Henn, 1985). Other oculomotor changes include hypometric saccades and disturbances of smooth pursuit (von Noorden et al., 1964; Burian and Burns, 1967; Lessell et al., 1971). Some authors have suggested a central origin for the eye movement disorders (von Noorden et al., 1964; Burian and Burns, 1967; Lessell et al., 1971; Emre and Henn, 1985) while others have considered that they are related to a more peripheral mechanism (Junge, 1966; Oohira et al., 1985).

We have investigated 26 MyD patients in whom we undertook routine neuro-ophthalmological investigation, EOG, visual evoked potential (VEP) and electromyographic (EMG) studies on the extraorbital muscles. VEP and EMG of the extraorbital muscles were examined to establish to what extent an afferent visual deficit and a myopathic disorder of the external ocular muscles, respectively, might be involved. One study (Gott et al., 1983) reported bilateral prechiasmatic VEP abnormalities in 17 MyD patients; no precise localization of the lesion was given. EMG of the external ocular muscles has revealed myopathic changes similar to those in the limb muscles, sometimes accompanied by myotonic discharges (Davidson, 1961; Zauberman and Magora, 1969). The primary objective of our study was to ascertain whether a characteristic pattern of subclinical oculomotor disorder could be detected in patients with MyD. Special attention was paid to the question of central versus peripheral pathophysiological mechanisms.

PATIENTS AND CONTROLS

Patients

Twenty-six patients with MyD, 15 males and 11 females, were studied, with an age range of 11–70 (mean 38) years. The duration of the clinical features, confirmed in all cases by EMG. A positive family history was present in all. None of the patients took any drugs which could influence myotonia, the EOG or VEPs.

Controls
Normal values were obtained from healthy control subjects recruited from the staff of the St. Elisabeth Hospital and their relatives. There were 25 control subjects for the VEP studies, matched for age and sex, and 20 for EOG also matched for age and sex.

METHODS

Routine neurological examination
This was performed with special attention to eye movements (saccades, on command and visually guided, smooth pursuit, myotonia), ptosis and specific MyD symptoms (muscle weakness, atrophy, myotonia).

Ophthalmological investigations
These included the measurement of visual acuity by an Oculus-Visutest apparatus which was expressed in decimal values, fundoscopy, extraocular movements and a slit lamp examination for lens opacities.

Electro-oculography
Eye movements were measured by d.c. electro-oculography (EOG). Non-polarizable miniature silver chloride skin electrodes were placed on the inner and outer canthi of the eyes to permit separate recordings for each eye. The signals from the electrodes were displayed on a ink-jet writing polygraph and analysed quantitatively with a PDP 11 computer. Patients were seated in a darkened room and their heads were stabilized by an occipital support.

Horizontal visually-guided saccades and horizontal smooth pursuit movements were studied. Targets for saccades consisted of red light-emitting diodes fixed on a cylindrical screen. The positions were 10 degr., 20 degr. and 30 degr. to the left and right of the primary position. Two different testing paradigms for saccades were used: (1) random stimulation with targets of variable amplitude; (2) stimulation with only the 20 degr. to the left and right in a predicted sequence. For random stimulation programme, only the 20 degree steps were analysed. The rate of target alternation in the predictive sequence had a pause of 3 s. A filter of 0–70 Hz and a sampling frequency of 512 Hz were used for the recording system. A complete saccade test consisted out of at least 20 steps of 20 degr. to both sides. The parameters studied included saccadic latency, maximum saccadic velocity (V max.) and amplitude. Smooth pursuit movement were elicited by a target moving on a dark background. The target was guided by a laser beam reflected by a mirror galvanometer. The target moved in a triangular wave fashion with excursions of 50 degr. (25 degr. left and right out of the midposition). The velocities varied from 30 to 50 degr./s. The filter range was 0–20 Hz. Smooth pursuit was quantitated by measuring the pursuit gain (the ratio of pursuit eye velocity/target velocity). Smooth pursuit gain was obtained by calculating the

gain, along a trajectory ranging from −15 degr. to +15 degr. from the midposition, between sample points with an interval of 0.02 s. The average gain of the velocities of 30–40–50 degr./s was determined.

VEP recording
VEPs were measured by a checkerboard method (Halliday, 1982) with 129 image reversals at a rate of 1 Hz, twice to the left and twice to the right. The checkerboard measured 27 × 31 cm. Each square subtended 48 min; the full field pattern was 10 degr. 25′. Full field luminance was 40 cd/m^2 with a background luminance of 0.05 cd/m^2. The recordings were performed with the subject seated in a dimmed room, 80 cm from the screen. Each eye was tested twice to ensure replicability of the wave form. The latencies were determined for the major occipital positive peak (P100).

Electromyography
Needle EMG of the levator palpebrae and the external recti was performed with special; attention to the insertion and spontaneous activity, the amplitude of motor unit potentials, myotonic discharges and voluntary recruitment pattern.

RESULTS

Neurological examination and ophthalmological investigation were undertaken in all cases. VEPs were recorded in 26 patients (100%), EOG in 18 (69%) and EMG in 17 patients (65%). The disorder varied in severity, being mild in 24%, moderate in 16%, moderate/severe in 28% and sever in 32% (Rankin disability scale). Clinically evident myotonia was demonstrable in the limb muscles in all cases. One patient showed an external ophthalmolplegia with limitations of external ocular movements. Bilateral ptosis in some degree was present in 17 cases (65%). Ophthalmological examination demonstrated impaired visual acuity in 18 patients (69%), Two patients had unilateral amblyopia, accompanied by a strabismus of less than 5 degr.; 5 patients had a decreased vision below 0.3, 1 unilaterally and 4 bilaterally. Cataract was found in 17 patients (65%) and typical myotonic butterfly-shaped macular dystrophy in 1 case. The reduced visual acuity was not always related to the cataract as this sometimes persisted after successful cataract excision. Ocular hypotonia was not found, nor was the disc pallor detected.

The results of the neurophysiological investigations are summarized in tables 1–3. Values in excess of 2 SD were considered as abnormal.

The P100 VEP latency was significantly prolonged in 64%, without obvious left-right differences, indicating a bilateral prechiasmatic abnormality. If corrected for a visual acuity above 0.3 the P100 was abnormal in 44%. The P100 latency did not correlate with age or presence of cataract; after surgery prolonged P100 latencies were also noted.

The EOG was significantly abnormal in 83% of the MD patients. The most striking disorder was a significant decrease of the maximum velocity of the visually-guided saccades (83%). The latencies of the saccades were slightly increased but compared with the controls this difference was not significant (figs 1,2). This prolongation was not significantly different between the first (mean latency: 242, SD 65.8), fifth (mean latency 253.6 ms, SD 74.9) and tenth (mean latency: 277.3 ms, SD 62.7) saccade in the predicted sequence trial.

No significant difference of latency was observed in the random trial saccades of different amplitudes: mean saccadic latency, following a 10 degr. saccade, was 267.8 ms (SD 65.1) and following a 30 degr. saccade 267.1 ms (SD 63.9). The amplitudes of the saccades were within normal limits (table 1). The latency of the P100 correlated significantly with the latency of the visually-guided saccades in the MyD group ($P = 0.01$; R value, 0.455) (fig. 3), while in the control group no significant correlation could be detected. Linear regression analysis of the EOG latency / VEP latency between patients and presumed normals showed no significant difference ($P = 0.09$). The Vmax. of the visually-guided saccades was not influenced by age, either for presumed normals or for MyD patients. The most striking finding was the significant ($P < 0.006$) difference in Vmax. of the visually-guided saccades between presumed normals (mean: 442.7 deg/s, SD 46.7) and MyD patients (mean: 309.7 degr.s, SD 43.2) (see fig. 2). This was independent of the testing paradigm. A substantial variation in amplitude of the saccades could not account for the decrease of Vmax. No central eye movement disorders such as dysmetria, nystagmus or gaze palsy were encountered. The smooth pursuit gain (the ratio

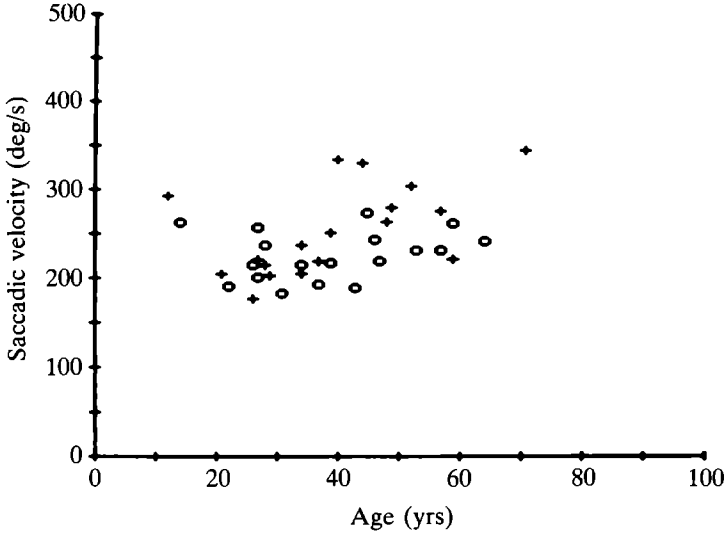

Fig. 1. Latency of visually-guided saccades of patients with MyD and age matched controls showing slightly prolongued latencies in the patient group although not significantly different from controls Patients (crosses), controls (open circles)

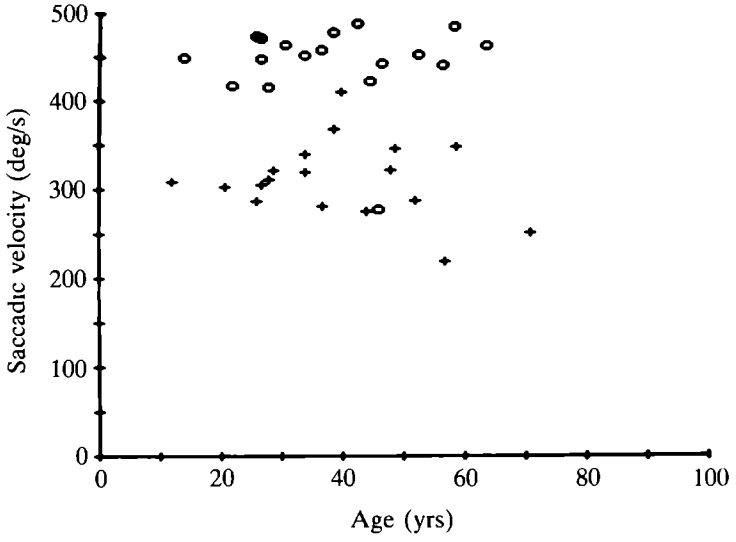

Fig. 2. Decreased Vmax. of the visually guided saccades of patients with MyD as compared with age-matched controls. Note the highly significant slowing of the saccade velocity in MyD patients (P<0.006) Patients (crosses), controls (open circles)

of pursuit eye velocity/target velocity) showed no significant abnormalities (see table 1).

Table 1. *EOG findings in patients with myotonic dystrophy*

	Controls		Patients		
	mean	SD	mean	SD	
Saccades					
Latency	225.1	27.7	252.7	50.4	P<0.107
Vmax.	442.7	46 7	309.7	43.2	P<0.006
Mean ampl.gain					
R eye	0 90	0 07	0.91	0.07	
L eye	0.85	0 07	0 90	0.08	
Smooth pursuit					
Mean gain (30-50 deg.)	0.82	0.14	0 72	0.22	P<0.131

The results of EMG of the extra-ocular muscles are listed in table 3. No neurogenic abnormalities were found and the recruitment pattern on maximum effort was within the normal range. The duration of the action potentials was rather short with a relatively low voltage. Myotonic discharges were regularly observed.

Table 3. EMG of the extraocular muscles in myotonic dystrophy

Insertion activity	myotonic discharges: 35%	
Action potential characteristics	LP ampl:mean: 560 μV (N=400-1200)	
Myotonic discharges	RE ampl:mean: 520 μV (N=300-1000)	
	LP duration:mean: 1.8 ms (N=1-3 ms)	
	RE duration:mean: 1.8 ms (N=1-3 ms)	
	LP: 0%	RE: 35%

LP = levator palpebrae. RE = external rectus. N = normal values.

DISCUSSION

Our results indicate the presence of a significant subclinical disorder of eye movement in patients with MyD (table 1). The most striking finding consist of a decrease of Vmax. of the horizontal visually-guided saccades compared with normal subjects ($P < 0.006$, Wilcoxon test), which does not correlate with age (fig. 4). This finding is in agreement with reports in the literature (Baloh et al., 1975; Oohira et al., 1985).

However, all other parameters for visually-guided saccades and the smooth pursuit movements are within normal limits, which is in contrast with most earlier reports in the literature (von Noorden et al., 1964; Burian and Burns, 1967; Lessell et al., 1971).

The latency of the visually-guided saccades is slightly increased, although compared with controls the difference is not statistically significant. This latency correlates with the latency of the P100 of the VEP ($P = 0.01$; R value 0.455; fig. 3) only for the patient group but not in the controls. However, no statistically significant difference could be detected between the groups, possibly due to the limited number of patients and based on a type II error. The prolonged latency of the saccades thus possibly reflects an afferent visual disturbance as an explanation. The bilateral prolongation of the P100 latency of VEP ($P < 0.001$, Wilcoxon test), suggest a bilateral prechiasmatic deficit (Table 2), the localization of which is uncertain (Gott et al., 1983).

Smooth pursuit eye movement are not significantly different from controls, as evidenced by the normal gain. In a number of cases a few catch-up saccades were seen. This phenomenon often indicates a reduced gain, but the smooth pursuit gain in our patient group was not significantly different form

Table 2. VEP in myotonic dystrophy

Myotonic dystrophy		
Age 11-77 yrs	Mean (R/L) 111/115 ms	SD 12/17
Controls		
Age 18-60 yrs	Mean (R/L) 100.8/100.9	SD 4.5/3.6

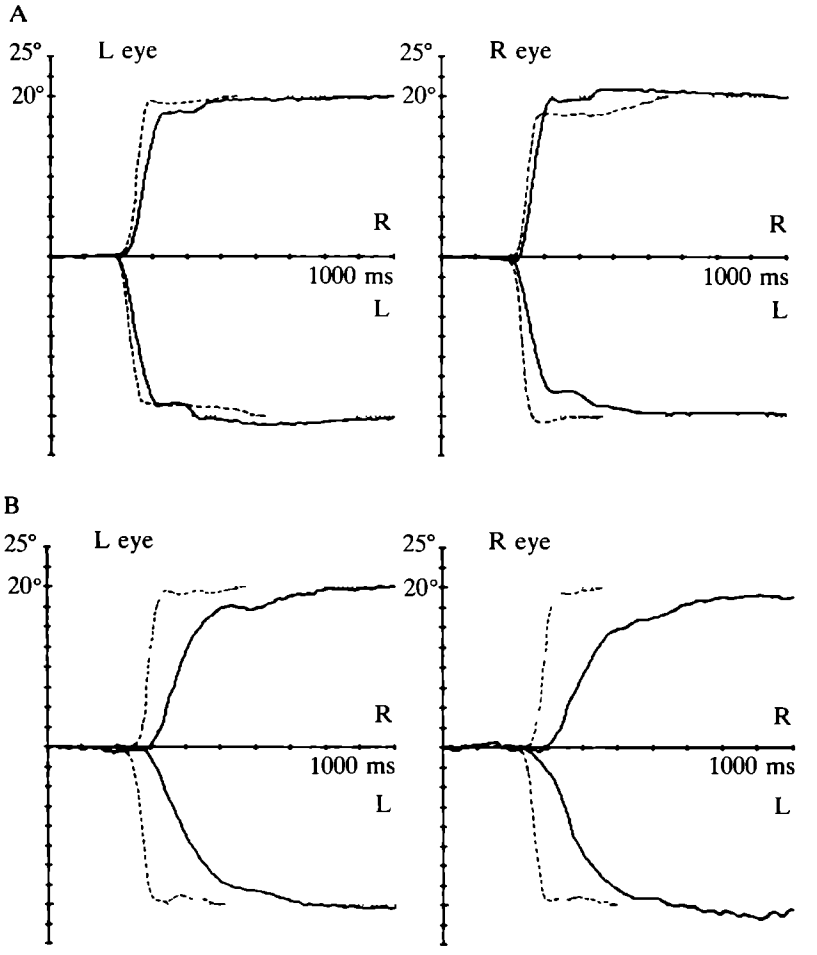

Fig. 4. Examples of recordings of visually-guided saccades of slighly affected (A) and severely affected (B) MyD patients, both compared with an age and sex matched control group (dotted line) Note the slow saccadic velocity

age-matched controls. Apparently our findings confirm the presumption of Oohira et al (1985) that MyD patients have a smooth pursuit gain that is within normal limits, although frequently interrupted by corrective saccades. This does not, however, always imply a CNS disorder (Schalen, 1980; Schalen et al., 1982; Leigh and Zee, 1983).

Abnormal smooth pursuit findings were the reason for previous authors considering the eye movement disturbances as being of central origin (von Noorden et al., 1964; Burian and Burns, 1967; Lessell et al., 1971). Disorders at different levels of the peripheral and central nervous systems have been described in MyD patients (Refsum et al., 1967; Lundervold et al., 1969; McComas et al., 1971; Ballantyne and Hansen, 1975; Panayiotopoulos and

Scarpalezos, 1977; Jamal et al., 1986), involving, for instance, the brainstem. This has been demonstrated by evoked potential studies (Thompson et al., 1983; Bartel et al., 1984). The slow saccades, as seen in our patients, may be due to a disorder of the saccadic burst cells in the pontine reticular formation (Leigh and Zee, 1983). However, the absence of abnormalities of eye movement with respect to saccadic latency and amplitude and normal smooth pursuit gain makes this explanation unlikely (Leigh and Zee, 1983). The same is true for a supranuclear deficit because this also leads principally to abnormalities of the latency and amplitude of saccades (Schiller et al., 1980). An ocular motor nerve paresis is characterized by slow hypometric saccades. The saccades become slower as they move in the field of action of the paretic muscle. This has not been found in our patients. The isolated finding of a decreased saccadic velocity in patients with MyD is therefore in favour of a peripheral myopathic pathophysiological mechanism. The EMG results (see Table 3) for the extraocular muscles demonstrating myopathy and myotonic discharges in a number of patients support this conclusion. The eye movement disturbances indicate a "dystrophic" rather than a myotonic abnormality. In the predictive sequence of the saccades there was no change during the block of trials and there was no significant difference of saccadic latency in the at random trial following saccades of different amplitudes.

The organization and structure of the extraocular muscles is quite different from that of other skeletal muscles in man (Miller, 1985). Different types of fibres are identifiable in human extraocular muscles by a variety of means, including light and electron microscopy (Kato, 1938; Dietert, 1965; Brandt and Leeson, 1966; Peachey, 1971; Bastiaensen, 1978), histochemistry (Ringel et al., 1978; Bormioli et al., 1979; Hoogenraad et al., 1979) and by pharmacological and electrophysiological properties (Scott and Collins, 1973).

According to Ringel et al. (1978), fibre types have been labelled based on histochemical features, as "coarse", "fine" and "granular". Coarse fibres, with a high myosin ATPase activity and high oxidative enzyme content, are predominant in the periphery of the extraocular muscles. Under the electron microscope these fibres show a "Felder Struktur", with large fields of myofibrils. The coarse fibres are supplied by many small calibre (gamma) nerve fibres with multiple "en grappe" nerve endings (Bastiaensen, 1978; Ringel et al., 1978). The fibres with a fine granular appearance (fine fibres) are more regularly distributed throughout the muscle and contain a moderate amount of myosin ATPase and oxidative enzymes. Granular fibres predominate in the central parts of extraocular muscles. They show a high myosin ATPase activity and a low oxidative enzyme content. On electron microscopy, these fibres show a "Fibrillen-Struktur" with grouped myofibrils. The granular and fine fibres are singly innervated by large motor neurons with "en plaque" nerve endings (Bastiaensen, 1978; Ringel et al., 1978).

The physiological action of the different extraocular muscle fibres correlates with the type of nerve endings seen by electron microscopy. The large (granular and fine) muscle fibres with en plaque nerve endings show fast

(twitch) activity as required saccades. The small (coarse) muscle fibres with "en grappe" nerve endings show a more tonic activity as required for smooth pursuit and the slow phase of nystagmus (Kato, 1938; Hess and Pilar, 1963; Bastiaensen, 1978; Ringel et al., 1978). The isolated decrease of Vmax. suggest a selective abnormality of the fibres with en plaque nerve endings.

The decrease of Vmax. with normal saccade amplitudes is in agreement with the results of Baloh et al. (1975) who tested 3 patients with MyD and stated that the mildest form of the disease, without any visual complaint, the ocular motor involvement consists of slowed saccades in patients who have full range eye movements. Exceptionally, external ophthalmoplegia or gaze palsy is caused by myotonic dystrophy (Lessell et al., 1971; Miller, 1985). One patient in this study clinically had an external ophthalmoplegia with marked slowed horizontal saccades and a limited range of eye movements in all directions. generally, the preservation of full range of eye movements separates the MyD group from the ocular myopathies.

Finally, there is a deficit in the afferent visual system, as shown by the VEP, in a large percentage of the patients, the lesion probably located prechiasmally. The exact localization of this disorder is topic of a current study.

Conclusions

The results of application of EOG, VEP and EMG studies to the extra-ocular muscles show clearly that subclinical disorders of eye movement are frequently present in MyD patients. These consist of an isolated decrease of Vmax. of the visually-guided saccades. As other parameters of saccades and smooth pursuit are within normal limits, this indicates a disorder of myopathic origin.

ACKNOWLEDGEMENTS

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CHAPTER 2.2

EYE MOVEMENT DISORDER: AN EARLY EXPRESSION OF THE MYOTONIC DYSTROPHY GENE?

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INTRODUCTION

Myotonic Dystrophy (MyD) is an autosomal dominant multisystem disorder with variable expressivity and reduced penetrance. Although generally regarded as a primary myopathy, MyD also affects both the central and peripheral nervous system (Jamal et al., 1986). Genetic counselling for affected individuals is usually straight forward. The risk for each offspring is 50%. On the other hand, absence of clinical signs and symptoms does not exclude the possibility that the person may be an asymptomatic carrier of the MyD gene.

In MyD the symptoms may appear at any age from infancy to old age (Griggs and Woods, 1989; Harper, 1989). The great majority of gene carriers may be detected in young adulthood if careful clinical examination is combined with EMG and slitlamp examination (Bundey, 1974; Harper, 1989; Polgar et al., 1972). It is currently unknown which proportion of gene carriers escapes detection at different ages. However, apparent nonpenetrance in adults does occur occasionally and for this reason additional tests are required for accurate counselling of asymptomatic individuals at risk.

The gene for MyD has been located on chromosome 19 through linkage with secretor, Lutheran and C3 (Eiberg et al., 1983) and the subsequent assignment of C3 to chromosome 19 (Whitehead et al., 1982).

Although the MyD gene itself has not been identified, several closely linked DNA markers are now available making an indirect diagnosis possible.

Presently, this diagnosis at the DNA level is possible in virtually all families with a suitable pedigree structure (Brunner et al., 1989a). Diagnostic sensitivity is usually over 95% and may be as high as 99% or higher if flanking markers are used. Such flanking markers have recently been defined (Brunner et al., 1989b; Korneluk et al., 1989).

Since DNA diagnosis is done by genetic linkage analysis of multiple family members, application of this technique may be precluded if other affected family members are unavailable for testing.

Although DNA diagnosis is highly sensitive, it is as yet not suitable as a simple, fast, low cost screening test of family members. Furthermore it gives no information about the expression of the MyD gene in terms of the start and course of symptoms. Rarely, false positive results may occur. In a previous study we have used infrared light eye movement registration (EMR) to show that over 80% of the classical patients have a significant decrease of the visually guided saccades (ter Bruggen et al., 1990). In the present study we have used EMR to study the eye movements of 5 asymptomatic MyD gene carriers, identified by DNA analysis, 7 mildly affected MyD patients and compared them with 23 healthy controls.

The purpose was to evaluate whether eye movement abnormalities are an early expression of the MyD gene and to determine the value of this procedure for presymptomatic detection of MyD patients.

PATIENTS AND CONTROLS

The patients were divided in two groups.
Group 1. Five asymptomatic MyD gene carriers (Rankin score 0: 2 males and 3 females) aged between 11 and 41 years (mean: 29 years). The diagnosis of MyD in all patients was made by DNA linkage analysis in their families.

Informative markers included ApoC2 (individuals 1, 2, 4 and 5) and CKMM (individuals 2, 3 and 4). These markers are located proximal to the MyD gene at 2–3 cM and 1 cM respectively. Flanking markers were used in two cases: RRAS (case 2) and KLK (case 5) which map at 8–10 cM distal to the MyD gene. Therefore, the predictive value of the DNA analysis was at least 97% in cases 1, 3 and 4 and well over 99% in cases 2 and 5. Clinical investigation, split-lamp investigation and electromyography (EMG) were performed in all cases. None of the gene carriers used any drug which could possibly influence myotonia or eye movement recordings (EMR).

Group 2. In addition seven mildly affected (Rankin score 1) MyD patients were studied, varying in age between 15 and 32 years (mean: 24 years). The duration of clinical symptoms varied from 1 to 15 years. The diagnosis in this group was made by the demonstration of myotonia and/or the typical dust-like cataract in combination with a positive family history for MyD. No drugs were used which are known to influence myotonia or the EMR registration.

Controls. Twenty three healthy, age and sex matched control subjects, varying in age between 22 and 34 years (mean:26 years) were recruited among the staff and their relatives of the St. Elisabeth and Maria Hospitals Tilburg, the Netherlands.

METHODS

Neurological examination was performed twice: once by the referring neurologist and once by the investigating neurologist (JB). Special attention was given to eye movements (saccades, on command and visually guided, smooth pursuit, myotonic reaction), signs of muscular dystrophy and myotonia.

Ophthalmological investigation was performed by one ophthalmologist (LB) and included assessment for ptosis, myotonic reaction of eye closure and investigation for lens opacities by slit lamp.

DNA investigation was performed as described previously (Brunner et al., 1989a, 1989b). Informative markers indicated the presence of the MyD gene with at least 97% reliability in all individuals in group 1.

Eye movement recording (EMR). The eye movements were measured by the infrared light method, according to the procedure described earlier (ter Bruggen et al., 1990). The following eye movements were studied: visually guided saccades and smooth pursuit movements. The visually guided saccades were measured with 20 degree steps in both at random and predicted

sequence. The smooth pursuit eye movements were registrated with 20, 30 and 40 degrees/sec. target velocity. Special attention was paid to latency of the saccades, saccadic amplitude and maximum velocity of the saccades. The smooth pursuit was expressed by the gain i.e. the ratio of pursuit eye velocity/target velocity.

Electromyography. All patients had previously been investigated for electrical myotonia by their referring neurologist.

RESULTS

Group 1. All five asymptomatic individuals scored optimal on the Rankin disability scale (Rankin score 0). No abnormalities were found on neurological examination. EMG investigation was normal in all these patients. Ophthalmological investigation demonstrated atypical lens changes in 4 individuals (see table 1A). The typical dustlike cataract was not seen in this group. The EMR results are summarized in table 1. No significant difference was found compared with controls (see fig. 1).

Group 2. All 7 mildly affected patients in this group scored Rankin score 1. Neurological abnormalities were slight (see table 2). Ophthalmological findings

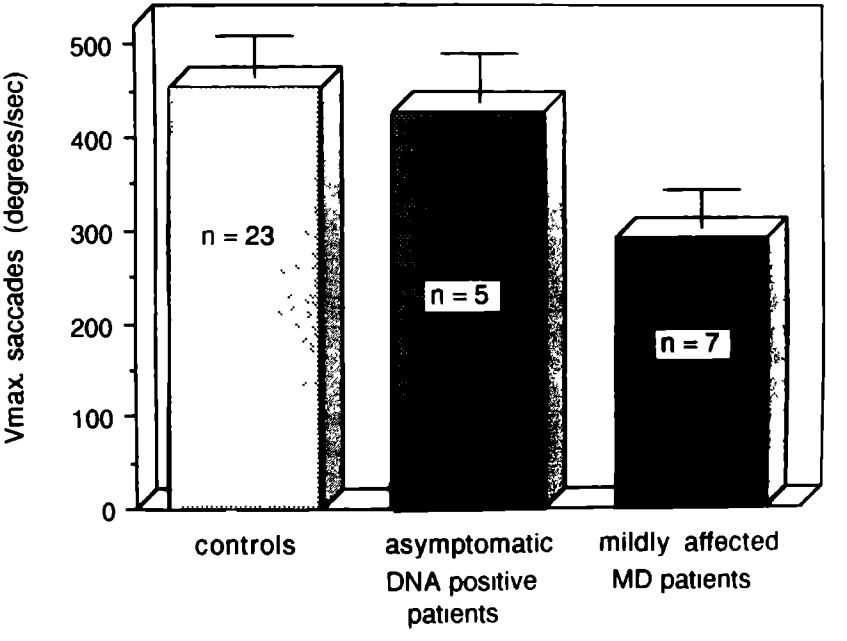

Fig. 1. Disorder of eye movement in myotonic dystrophy The mean maximum velocities of the visually guided saccades is plotted for asymptomatic DNA positive myotonic dystrophy individuals, mildly affected patients and controls (SD is graphically expressed)

Table 1. EMR findings in asymptomatic gene carriers (group 1) and mildly affected MyD patients (group 2)

	Group 1 (N = 5) asymptomatic MyD patients		Group 2 (N = 7) mildly affected MyD patients		Controls (N = 27)	
	Mean	SD	Mean	SD	Mean	SD
Saccades						
Vmax	453	61	305*	38	451	41
Latency	211	22	246	45	223	28
Amp gain						
R eye	0 93	0 09	0 95	0 03	0 90	0 07
L eye	0 94	0 03	0 94	0 05	0 86	0 07
Smooth pursuit						
Mean gain						
20 deg	1 17	0 14	1 12	0 12	0 78	0 13
30 deg	1 11	0 15	1 07	0 13	0 86	0 10
40 deg	1 03	0 24	1 02	0 16	0 89	0 10

*Significance $P < 0.01$ compared to controls by Wilcoxon test

Table 2. Neurological and slitlamp investigation of 7 mildly affected MyD patients

	Patients No						
Weakness/disorder	6	7	8	9	10	11	12
Facial wk	+	+	+	–	–	+/–	+/–
Levator palpebra wk	+/–	+	+/–	+/–	+/–	–	+/–
Masseter wk	+/–	+/–	+/–	+/–	–	–	–
Orbicularis oris wk	+/–	+/–	–	–	–	–	–
Sternocleido wk	+/–	+/–	+/–	–	+/–	–	–
Shoulder girdle wk	–	–	–	–	–	–	–
Pelvic girdle wk	–	–	–	–	–	–	–
Prox limb muscle wk	–	–	–	–	–	–	–
Dist limb muscle wk	+/–	+/–	+/–	–	+/–	+/–	+/–
Myotonia limbs	–	+	+	+	+	+	+
Eye lid myotonia	–	–	–	–	–	–	–
Eye movement disorder	–	–	–	–	–	–	–
Slitlamp invest	dc*	n*	ccp*	dc*	dc*	ccp*	n*

+ sign unequivocally present, +/– sign present but minimal, – sign absent, dc typical dustlike cataract, cpp crystals in the posterior part of the lens, wk weakness, * both eyes, n normal

were normal in 2 and atypical for MyD in another 2. The typical dustlike crystals were seen in 3 patients (see table 2).

All of the patients except patient 6 showed electromyographical myotonia (table 2). However, this individual showed mild muscular weakness and typical myotonic cataract. The EMR results are summarized in table 1. The maximum velocity of the visually guided saccades (Vmax.) was significantly different compared to the Vmax. of the controls ($p < 0.01$, Wilcoxon test).

DISCUSSION

In this study the question was addressed whether the eye movement disorder would be an early expression of the MyD gene. The external ocular muscles are commonly affected in MyD, but signs and symptoms directly attributable to extraocular muscle weakness such as diplopia are uncommon (Griggs and Woods, 1989; Harper, 1989; ter Bruggen et al., 1990). Because the infrared method is very sensitive for measuring eye movement disorders, subclinical abnormalities can be discovered. To our knowledge this is the first report concerning the value of precise eye movement recording for early diagnosis of MyD.

Although the numbers are still small our results indicate that the extraocular muscles are affected frequently and early in the course of MyD (see table 2). The eye movement abnormality is characterized by an isolated decrease of Vmax. of the saccades with normal amplitudes. The EMR findings are most compatible with a myopathic etiology (Baloh et al., 1975; Oohira et al., 1985; ter Bruggen et al., 1990). The comparison of the main sequence (i.e. the relationship between amplitude magnitude and maximum velocity of the saccades) between other extraocular myopathies and MD also supports this assumption (Oohira et al., 1985). Accordingly light and electron-microscopical studies show myopathic abnormalities of the extraocular muscles in MyD (von Noorden and Allen, 1964; Ketelsen and Schmidt, 1972; Kuwabara and Lessell, 1976; Isahiki et al., 1989; ter Bruggen et al., 1990).

In the present study eye movement recordings of all patients in the minimally affected group showed a significant decrease in the maximum velocity of the saccades ($p < 0.01$, Wilcoxon test) without other oculomotor abnormalities. These results confirm the findings of a previous study (ter Bruggen et al., 1990). This indicates that eye movement disorders occur early in the course of the disease and perhaps even may precede the onset of detectable skeletal muscle weakness or myotonia. Since we did not find signs of disturbed eye movements in our asymptomatic group, EMR recording does not appear a more sensitive diagnostic tool in those cases in which neurological examination and EMG are negative.

So far, we have studied only a limited number of cases. Also DNA linkage analysis alone cannot prove that a given person is a gene carrier. Thus, not all individuals in the asymptomatic group may truly carry the MyD gene, even though their individual likehoods of being a gene carrier are high and 4 out of 5 showed aspecific lens changes. Because of these limitations we think that additional studies, aiming at preclinical diagnosis of MyD with EMR are still warranted.

Exclusion of the MyD gene in an at risk individual can best be accomplished by a combination of careful neurological and ophthalmological examination, EMG recording and DNA analysis. In those cases where the DNA analysis suggests the presence of the MD gene in the absence of clinical symptoms, two approaches may be used simultaneously. Flanking DNA markers can

enhance the accuracy of the DNA diagnosis. Reevaluation of the clinical data is mandatory and additional clinical testing should be considered. In this setting, repeated EMG registration and EMR are possible useful options.

The EMR abnormalities in MyD appear rather specific for this disorder (ter Bruggen et al., 1990). The combination of slow saccades and normal amplitudes in both horizontal directions is unusual for ocular myopathies, while several central abnormalities with slow saccades show more extensive disturbances (Leigh and Zee, 1983; Stell et al., 1989).

Since the decrease of Vmax. is found in well over 80% of the symptomatic MyD patients (ter Bruggen et al., 1990), this sign may be useful in the evaluation in patients in whom MyD is suspected but not certain. This applies to the isolated patient with myotonia and minimal weakness as well as to familial cases with distal muscle weakness but no detectable myotonia (pat. 6) or eye abnormalities. A recent study of 602 individuals in 88 MyD kindreds revealed 130 individuals (21.5%) with equivocal or unspecific signs (Mathieu et al., 1989). In such cases EMR should be considered.

We conclude that eye movements are significantly and early disturbed in the course of MyD. Eye movement registration (EMR) detects a rather specific pattern of abnormalities, consisting of a decrease of Vmax without other abnormalities.

EMR has so far no proven additional value for the detection of gene carriers, that are asymptomatic with currently accepted techniques.

CHAPTER 2.3

MYOTONIC DYSTROPHY: THE NATURAL HISTORY OF EYE MOVEMENT DISORDERS

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INTRODUCTION

Eye movement disorders are a common and rather early subclinical sign in myotonic dystrophy (MyD) (ter Bruggen et al., 1990; ter Bruggen et al., 1992). Diplopia is uncommon and external ophthalmoplegia even exceptional (ter Bruggen et al, 1990, 1992). A significant decrease of the maximum velocity of visually guided saccades has been reported for the classical form (ter Bruggen et al., 1990); a recent study indicated a derangement of smooth pursuit as most pronounced feature (Oohira et al., 1985). Some authors advocate a mere peripheral (Oohira et al., 1985; ter Bruggen et al., 1990) while others presume a central pathophysiological mechanism (van Noorden et al., 1964; Burian and Burns, 1967; Lessel et al., 1971; Bollen et al., 1992). So far no studies have been reported to outline the natural history. Therefore we performed a follow up study of eye movements in 6 patients with the classical form of MyD 6 years after a previous study (ter Bruggen et al., 1990).

PATIENTS AND METHODS

Patients

The patients in this study are members of kindreds with classical MyD in accordance with published criteria (Griggs et al., 1989). All patients were classified as adult onset and were gathered out of a previously studied group in 1985–1986 (ter Bruggen et al., 1990). None of the patients had important other diseases, signs of a mental disorder or used any drugs which could influence myotonia, electro-oculography (EOG) or VEP.

Methods

The severity of the limb muscles was scored according to an international rating-scale put forward by Mathieu (Mathieu et al., 1992) and by Karnofsky (Karnofsky and Burchenal, 1949) and Rankin disability scales.

Besides, the same protocol as in a previous study (ter Bruggen en et al., 1990) was used for neurological and ophthalmological investigation. Furthermore eye movements (Vmax and latency of 20 degr. horizontal visually guided saccades and mean gain of 30–40–50 degr./sec. smooth pursuit) and VEP P100 latency were studied conform the previous study (ter Bruggen et al., 1990).

Statistics

The differences between the two time points (1985–1986 and 1992), were evaluated by CIA-statistics: Wilcoxon paired ranksum test and Spearman correlation coefficients (Gardner and Altman, 1986).

RESULTS

The most important results are listed in table 1.
The group consists of 3 men and 3 women, with a mean age of 40.2 years (range 27–65). Neuromuscular involvement was as follows: 2 patients were rated Mathieu II (minimally affected) and the remaining 4 Mathieu III (moderately affected) (Griggs et al., 1989). In a period of about 6 years one patient got mild clinical signs of an external ocular weakness without diplopia. There was a clear progression of the decrease of Vmax of the visually guided saccades ($p < 0.01$, Wilcoxon) and VEP P100 latency prolongation ($p < 0.05$, Wilcoxon). No significant left-right differences could were observed for V max. As to be expected , all parameters for limb weakness showed more or less worsening ($p < 0.01$, Wilcoxon). In comparison to our previous study (ter Bruggen et al., 1990) no significant differences could be found for latency of the visually guided saccades or for the mean gain of smooth pursuit. The latter results did not differ from controls either (ter Bruggen et al., 1990). Despite the small group a significant correlation was found for Vmax and Mathieu (limb weakness) score ($R = -0.5$ Spearman, 95% CI: −0.748 to −0.112). Differences of disability scales did not show any significant correlations with the decrease of Vmax. of the saccades.

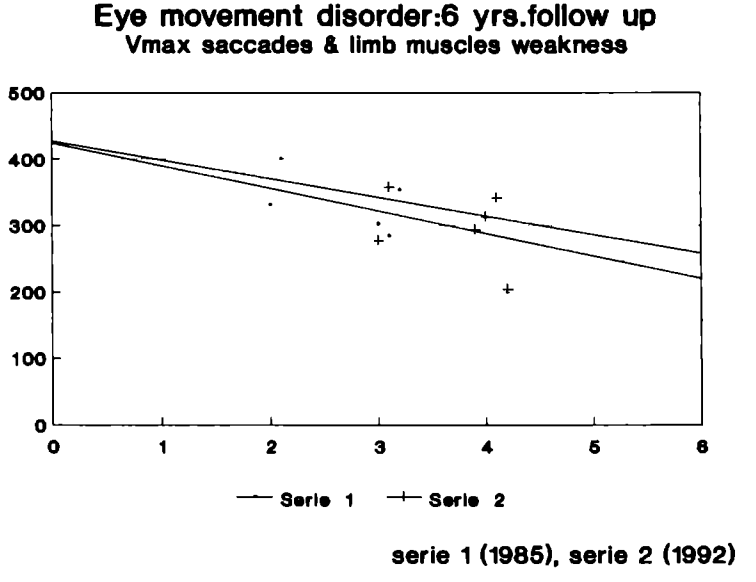

Fig. 1. The relationship of decrease of the maximum velocity of the saccades and weakness of the limbs is depicted (Mathieu-score). Serie 1 represents the values in 1986 and serie 2 those of 1992. The drawn line indicates the progression rate in 6 years time in this adult onset group of MyD (slope: −0.003).

DISCUSSION

One of the hallmarks of MyD is the progressive weakness and atrophy of limb muscles. Although extra-ocular muscles are quite different as regards histological structure this study demonstrates a progressive decrease of Vmax of the horizontal saccades, correlating with the progression of limb weakness (Mathieu-score). The Vmax decrease reflects myopathic changes in the extra-ocular muscles perhaps influenced by central adaptation mechanisms (Ter Bruggen et al., 1990, 1992; Verhagen et al., 1992). Therefore the data support a progressive involvement of the extra-ocular muscles in the course of time (fig. 1), exceeding the normal aging (Warabi et al., 1984).

All other eye movement parameters were normal, including smooth pursuit gain. Central abnormalities, based on an altered smooth pursuit gain (Bollen et al., 1992) could not be demonstrated in this study. Another finding was the progressive prolongation of VEP P100 latency ($p < 0.05$), exceeding the normal age related prolongation (Celesia and Daly, 1977). No relationship could be found between VEP latency and saccadic latency, in contradiction with previous results (ter Bruggen et al., 1990).

In conclusion, the functional abnormality of the extra-ocular muscles is progressive, correlating with the severity of limb weakness. Furthermore both afferent (VEP) and efferent systems (EOG) deteriorate in a course independently to one another (ter Bruggen et al., 1990).

	1986	1992
Rankin (1–5)	1	2**
Karnofsky (0–100)	90	70**
Mathieu-score (1–5)	3	4**
visus	0.9	0.8
clin.extra-oc.wkn	N = 0	N = 1
slitlamp	N = 1	N = 1
normal	2 (+)	1 (++)
ccp (+−++++)	0	1 (+++)
pcc (+−++++)	2	1
cat.	1	1
dense cat.	0	1
lens extr.		
Saccades (20 deg)		
Vmax. (deg/s)	335	280**
	(SD 59.8)	(SD 71.1)
latency (ms.)	236	239
	(SD 57.9)	(SD 56.3)
Smooth pursuit	0.82	0.86
mean gain	(SD 0.14)	(SD 0.27)
(30–50 deg/s)		
VEP P100	108	118*
latency (ms)	(SD 15.8)	(SD 19.5)

Expressed values are the means of the results of the separate groups Statistics refer to Wilcoxon paired ranksum test.

EOG:	electro-oculography
clin.extra-oc.wkn	clinical extra-ocular weakness
ccp:	crystals cortex posterior
pcc:	polychromatic crystals or iridescent lucencies
+−++++:	semi-quantification
cat.:	cataract
dense cat.:	dense cataract
*:	$p < 0.05$ Wilcoxon difference 1986–1992
**:	$p < 0.01$ Wilcoxon difference 1986–1992

CHAPTER 2.4

FOVEAL PHOTOPIGMENT KINETICS-ABNORMALITY: AN EARLY SIGN IN MYOTONIC DYSTROPHY?

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INTRODUCTION

Myotonic Dystrophy (MyD) or Curschmann-Steinert disease is an autosomal dominant multisystem disorder of which the gene abnormality is localized on chromosome 19 (Brunner et al., 1989; Harper, 1989). DNA diagnosis of MyD is possible with both sensitivity and specificity higher than 96% (Brunner et al., 1989). It shows variable gene penetrance and expressivity, and the onset of MyD varies from early infancy to old age (Polgar et al., 1972). An alteration in the intrinsic biochemical composition of the cell membrane, affecting the entire body, has been proposed as the pathogenesis of MyD (Harper et al., 1989).

Ocular abnormalities associated with MyD are cataract, hypotonia and chorio-retinal changes. Several authors reported the considerable electroretinal alterations in MyD patients, even before fundal changes and other expression of the abnormal gene (Junge, 1966; Burian and Burns, 1967; Stanescu and Wawernia, 1970; Stanescu and Michiels, 1975; Kirkham and Coupland, 1981; Gott et al., 1983; Creel et al., 1985; Harper et al., 1989; Sandrini et al., 1986; Pinto et al., 1987; Kerty and Ganes, 1989; ter Bruggen et al., 1990). A common finding was the reduction of the b-wave amplitude in ERG, both in scotopic and photopic conditions (Junge, 1966; Burian and Burns, 1967; Stanescu and Wawernia, 1970; Stanescu and Michiels, 1975; Kirkham and Coupland, 1981; Gott et al., 1983; Creel et al., 1985; Sandrini et al., 1986; Pinto et al., 1987). VEP recording in MyD repeatedly showed prolongation of latency or decrease of amplitude (Pinto et al., 1987). They recorded PERG and pVEP simultaneously and found abnormalities that occured independently of one another. The authors also found subnormal EOG Arden indices. They suggested that the pathological process may affect both the retina and post-retinal intrinsic visual pathways.

Both clinical (Junge, 1966; Burian and Burns, 1967) and histopathological (Manschot, 1968; Burian and Burns, 1966; Burns, 1969; Houber and Babel, 1970; Betten et al., 1971; Ginsberg et al., 1978; Hayasaka et al., 1984; Sarks et al., 1985) evidence of photoreceptor and other neuroretinal abnormalities has been reported in progressive stages of MyD. The purpose of this study was to investigate the early expression of retinal abnormalities in MyD, including those of foveal photoreceptors. We have used retinal densitometry to examine the macular photoreceptors of eyes of a group of minimally affected MyD patients. To our knowledge this technique has never been utilized in Myotonic Dystrophy.

MATERIAL AND METHODS

Subjects

Twelve patients, 8 females and 4 males, were examined.

Informed consent was given by all patients. They all either had a positive family history for MyD and myotonia, or a clinical diagnosis of MyD,

confirmed by DNA investigation (Laboratory of Clinical Genetics, Radboud Hospital, Nijmegen, the Netherlands). All patients were submitted to neurological and ophthalmological examination, including testing of visual acuity, fundoscopy, slit-lamp examination and tonometry (Goldmann applanation tonometer). Inclusion criteria for the study were a visual acuity of at least 0.8 after correction and no or minimal lens abnormalities (sporadic polychromatic cristals or white dots) and a Karnofsky index exceeding 80. An age matched group of 12 healthy subjects was used as control.

Investigations

Densitometry

The density of foveal cone pigments was measured with the Utrecht densitometer which has been described in detail by van Norren and van der Kraats (van Norren and van der Kraats, 1989).

Briefly, the light reflection at the fundus is determined at a range of wave lengths through the visual spectrum. The light needed for this measurements is so dim that influence on the visual pigments is minimal. The spot of light/ (30-W halogen lamp) at the fundus is restricted to 2.8 degrees in this measurement. Reflections of the fundal lights are collected by a photo-multiplier in photon-counting mode and processed by a computer. Bleaching is possible with a separate light path which provides a retinal illumination of 5.6 log Td. The change in reflection from the retina of a healthy person before and after bleaching determines the "two-way density". The pupils of all subjects were dilated with tropicamide. A bar made of dental impression compound, and two temple pads were used for immobilization of the head. The fundus camera was adjusted to obtain the highest possible reflection as measured by the photomultiplier. Subjects fixated cross-hairs centered with the stimulus field. The fovea was bleached for 2 minutes. After switching off the bleaching light, the regeneration of cone pigment was followed until the density trace had reached a stable level. Then the bleaching light was switched on again for 2 minutes. The density trace should than return to the fully bleached condition, permitting the reliability of the measurements to be checked. The changes in retinal transmittance between fully dark adapted and fully bleached states of the retina are related to the photopigment density of the test area.

Basically, two values can be extracted from the data: the density difference and the time constant of pigment regeneration. The density difference is the change in the logarithm of the measuring light reflectance to the reference light reflectance, from fully bleached to fully adapted states. The time constant of pigment regeneration can be estimated from the initial 180 sec. of adaptation following extinction of the bleaching light.

In this study we only present the data obtained at 554 nm, being the peak of the absorption-spectrum. Peripheral measurements, investigating the rods

take considerably longer, since the adopser regenerates slow. In our subjects occasionally denture fitting problems and lack of concentration – common signs of MyD – interfered with the measurements.

VEP and ERG
Pattern visual evoked potentials (VEP) and electroretinography (ERG) measurements were made with a laboratory built system for clinical electrophysiology of vision (Van Norren and van der Kraats, 1984). ERG was performed in both scotopic and photopic conditions, using corneal electrodes and three different white light stimulus intensities. VEP recording was done under standard conditions, using 11', 46' and 92' settings in the black-and-white checkerboard reversal pattern.

Anomaloscope
Colour matching was investigated with a Nagel type I anomaloscope by a standard technique (Pojorny, 1979).

RESULTS

The ages of the patients ranged from 12 to 39 years (mean: 26 yrs) and the general disability rated by Karnofsky index (25) varied from 80 to 100 (mean: 90). The duration of clinical disease varied from 0 to 408 months (mean: 71 mths).

A summary of the main ophthalmological results is displayed in table 1. Slit-lamp examination revealed minimal lens opacities in four patients (30%) and characteristic polychromatic crystals in three patients (25%), whilst in five patients (42%) no abnormalities were detected. Fundoscopy did not show morphological changes of the retina in any of the patients. The visual acuity varied from 1.2 to 0.8 (mean: 0.9). Anomaloscopy showed no protan or deutan defects. Seven out of nine patients had low intra-ocular pressures bilaterally, whilst two patients had low-normal pressures (mean: 12.7 ± 2.3) (normal values: 15.5 ± 2.5) (Goldman and Schmidt, 1957).

In 4 out of 23 eyes (17%) the scotopic ERG showed a significant decrease of the a-wave amplitude and in only 1/23 eyes (4%) a significant decrease of the b-wave. An increase in implicit time was noticed in 10/23 eyes (43%) for the scotopic a-wave and 3/23 (12%) for the scotopic b-wave. In photopic conditions 8/23 eyes (35%) showed a decrease of the a-wave amplitude and in 7/23 eyes (30%) a decrease of the b-wave amplitude. An increase in implicit time was recorded in 2/23 (8%) eyes for the photopic a-wave and in 4/23 (16%) for the photopic b-wave.

Pattern VEP recording with 11' pattern reversal blocks showed a significant prolongation of the P100-latency in 4 patients (30%). In 5 eyes (42%) a decrease of the VEP amplitude was noted. No significant hemispheric asymmetry was seen. In 2 eyes (16%) both VEP amplitude and latency were abnormal. Only

Table 1. Ophthalmic findings in myotonic dystrophy

patient	duration (months)	vision right	vision left		densito right	densito left	scotERG amplitude A	scotERG amplitude B	scotERG latitude A	scotERG latitude B	photERG amplitude A	photERG amplitude B	photERG latitude A	photERG latitude B
1. AB*	12	1.0	1.0	cp	–	0.21	–	N	–	N	L	L	N	H
2. AB	24	1.0	0.8	vac	0.22	0.18	N	N	N	N	L	L	N	N
3. GF*	60	1.0	1.0	pcc	0.25	–	N	N	N	N	–	–	–	–
4. EG	144	0.8	1.0	dots	0.35	0.37	N	N	H	N	N	N	N	N
5. JM*	0	1.2	1.2	dot	0.21	–	–	N	–	N	L	N	N	H
6. JM	0	0.9	0.9	N	0.33	0.35	N	N	N	N	N	N	N	N
7. JS	408	0.6	0.6	dcp	0.37	0.40	N	N	H	N	N	N	N	N
8. JS	118	1.0	1.0	cp	–	0.23	N	N	N	N	N	N	H	N
9. JS	72	1.0	1.0	dcp	0.36	–	L/N	N	H	N	N	N	N	N
10. JV	19	1.0	–	dot	0.18	–	L/N	L/N	N	H/N	L/N	L/N	N	N
11. MV	0	1.0	1.0	dots	0.12	–	N	N	H	N	L/N	L	N	N
12. GY	0	0.9	0.9	N	0.39	0.43	L	N	H	N	N	N	N	N

N: normal, L: decreased; H: prolongued or increased; –: no result; pcc: polychromatic crystals; cp: crystals in lens cortex posterior; dots: dots in lens cortex posterior; dcp: dot(s) and crystals in lens cortex posterior; densito: foveal two-way densities; normal: age matched: 0.38 +/– 0.12

(*) values of peripheral densitometry
pat 1: 0.20 (N)
pat 3: 0.13 (abnormal)
pat 5: 0.17 (N)

five eyes (42%) had normal VEP data. There was no clear correlation between VEP and ERG data.

Foveal densitometric measurements showed in 6 patients (50%) a significant decrease of the two-way density. The mean density of all patients tested (0.29 +/− 0.09) was significantly lower than the mean of the age-matched control group (0.38 +/− 0.12). The time constants of pigment regeneration of the patients (mean: 66 +/− 6 sec) were in the normal range (mean: 69 +/− 8 sec). Both peripheral retinal densitometry and ERG in patient 1 and 5 showed no abnormalities, but foveal densitometry was significantly abnormal in both cases. In patient 3 the peripheral densitometric measurement was low: 0.13 (normal: 0.18 +/− 0.04) (table 1).

The Arden-index, of the EOG was subnormal in 6/12 eyes (mean: 181% +/− 15.7, range: 161–193).

Myotonia was noted in 7 patients (58%). Ptosis was absent in 6 patients (50%), minimal in one (8%), moderate in 3 patients (25%), and severe in the remaining 2 patients (16%). Weakness of the limb muscles was found in 3 patients (25%), varying from minimal to moderate.

DISCUSSION

Foveal densitometry demonstrated subclinical abnormalities of foveal photoreceptors in 50% of our patients with minimal (early) expression of the MyD gene (table 1). Even in a 12 year old asymptomatic DNA-positive individual (pt.11) a strikingly abnormal value was noticed. The reduced two-way density may be caused by loss or dysfunction of photoreceptors or by a reduced effective optical density of foveal cones due to shortened outer segments. Other causes include active or chronic serous leakage of subretinal fluid with photoreceptor disorientation and abnormally high stray light levels secondary to lenticular opacities. The latter is unlikely because lens opacities in our patients were neglidgable. Serous leakage of subretinal fluid can be excluded by normal fundoscopy findings. The results of the normal pigment regeneration times excludes serous leakage because this phenomenon is usually associated with increased pigment regeneration times (van Meel et al., 1986). Normal findings with the Nagel anomaloscope, which would be most sensitive to cone pigment density changes occuring in individual cones, such as shortened outer segments (Alpern, 1979), make such alterations less probable. Therefore, we argue in favour of loss or dysfunction of photoreceptors to explain the reduced densitometric values.

Additionally, the peripheral retina of three cases was examined using retinal densitometry. Whilst in all three patients the foveal densitometry findings were abnormal, in two out of three the peripheral two-way densities were normal. Although the number of investigated eyes is limited, these findings may indicate predominant involvement of the macular area in early stages of MyD. The predictive power for densitometry for family-members of patients

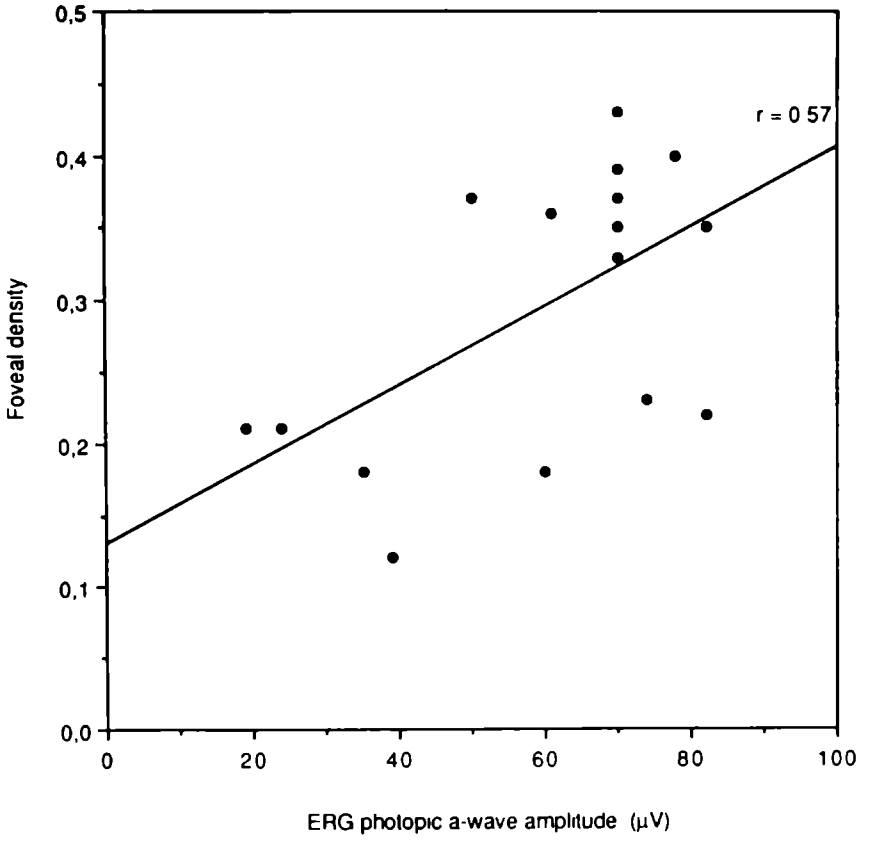

Fig. 1. The amplitudes of the a wave of the photopic ERG are plotted against the values of foveal densitometry The best fitting line has a R-value of 0 57 (Spearman's rank corr) and a P = 0 02 (Wilcoxon rank sum test) to reject the nul-option

with MyD is very high (odds ratio: 6, 95% CI: 0.728 – 277 CIA statistics) compared with the total of all performed ophthalmological tests (odds ratio: 10, 95% CI: 1.42 – 442).

In contrast with previous authors (see introduction), who reported reduced amplitudes of the scotopic b-wave as the most frequent ERG abnormality, our study showed a significant predominance of *photopic* ERG a- and b-wave abnormalities. The latter is not due to a sample error. Compared with the study of Pinto (1987) a difference of proportions is significantly different (difference of confidence interval: 0.560, 99% CI: 0.151 – 2.58, CIA statistics).

Furthermore, the photopic ERG a-wave amplitude showed a significant (Wilcoxon: $p = 0.02$) correlation with the foveal densitometric values. The decrease of amplitude of 11' p-VEP shows a trend for correlation with foveal densitometric findings (Wilcoxon, $0.05 < p < 0.10$). These findings also points at subclinical (macular) cone changes in early onset of MyD. Only in a minority of this selected patient group, a decrease of the b-wave of the

scotopic ERG could be detected (table 1). Presumably, the scotopic b-wave abnormality seems a late manifestation (Sarks et al., 1985). Several authors described a decrease of the scotopic b-wave (Faber, 1969; Miller and Dowling, 1970), which may be associated with a disturbance in retinal Mueller cells. Another report (Pinto et al., 1987) suggested involvement of ganglion cells. Retinal pigment epithelial changes have been clinically (Junge, 1966; Burian and Burns, 1967; Babel and Tsacopoulos, 1970) and histologically observed (15–18). Whether the photoreceptor and other neuroretinal (Mueller and ganglion cells) alterations are primary or secondary to changes in the retinal pigment epithelium (RPE), remains a matter of discussion. Sarks (1985) argues in favour of the principal pathological changes to occur at the level of the RPE, based on the minimal fallout of photoreceptors, despite relatively good vision and slightly affected electrophysiological tests. Whilst, in those cases the RPE was grossly irregular and hypertrophic, with distorted villi, containing – in particular under the fovea – large amounts of (melano)lipofuscin (Sarks et al., 1985). If the EOG is abnormal, a much larger area than the foveal (receptors) must be affected (see above). It is intriguing to speculate that in MyD some as yet unknown metabolic disturbance of the RPE cells may result in dysfunction and subsequent variable atrophy of photo-receptors.

Where does this leave us with the retinal pathophysiology?

The difficulty could lie in the voltage generating mechanisms of the slow oscillations at the basal membrane, the concentration of the 'light peak substance (l.p.s.)' at the level of the photoreceptors or the transmittance of the message across the apical membrane through the RPE cytoplasm to the basal membrane. Less likely hypotheses, we cannot exclude, are a delay or a block in the messenger system or a defective voltage generation system of RPE and photoreceptors, similar to the one demonstrated in the muscle- and erythrocyte membranes. Nevertheless, the 'l.p.s.' concentration change-abnormality at the level of the photoreceptors (Gallmore etal., 1988) might explain both ERG, EOG and densitometry findings. Therefore, we postulate an abnormality in a Na, Ca:K dependent exchanger in the outer segments to be the primary defect, taking in account knowledge of membrane pathophysiology. The mRNA of the MyD gene encodes a protein kinase polypeptide, which is known to modulate the activity of excitable cells by phosphorylation of ion-channels (Brook et al., 1992; Hunter, 1991). The (muscle) membrane has a decreased resting potential, with a value close to the threshold for activation of Na+ channels and the presence of specific (apamin-sensitive) Ca++-activated K+ channels (Schmidt-Antromarchi et al., 1985; Ruedel et al., 1989). Besides, the Na+-K+-ATP-ase activity is decreased and the voltage dependent Ca++ channels are active under conditions in which they are normally inactive (Benders et al., 1990). Therefore, instead of 3 moles of Na+ ion exchange for 2 moles of K+ ion in control cells, a 2 Na+ for 2 K+ ion exchange occured in MyD cells (Hull and Roses, 1976). Altered inward sodium transport and extracellular leaking of potassium is involved in the generation of action potentials or regulation of resting potentials (Desnuelle et al., 1982; Dowling

et al., 1987; Wevers et al., 1990; Kuwabara et al., 1991). The defective regulation of ion transport could initiate or contribute to abnormal cellular functions in MyD (Wevers et al., 1990). Remarkably, in more advanced disease the Mueller glial cell becomes affected. In particular this cell, with a high resting potential, appears to be most sensitive to potassium changes at physiological levels compared with neurons (Dowling, 1987). We hope that future studies may obtain additional information on the locality and mechanisms of the retinal dysfunction in MyD.

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CHAPTER 3.1

OCULOMOTOR, AUDITORY AND VESTIBULAR RESPONSES IN MYOTONIC DYSTROPHY

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INTRODUCTION

It is well-known that myotonic dystrophy (MyD) is a progressive autosomal dominant multisystem disorder (see Kuhn and Fiehn, 1981 and Miller, 1985 for review). The associated gene defect, i.e. an unstable DNA segment in affected subjects, has been recently identified within the region of the MyD locus on chromosome 19 (Aslanidis et al., 1992). Neurophysiologic studies on MyD have produced evidence for peripheral and central involvement. Evidence for peripheral involvement has come from studies employing electromyography (EMG) (Davidson, 1961; Lessel et al., 1971; Caccia et al., 1972; Panayiotopoulos et al., 1977; Oohira et al., 1985; Jamal et al., 1986; ter Bruggen et al., 1990), somatosensory-evoked potentials (SSEPs) (Bartel et al., 1984), visual-evoked potentials (VEPs) (Gott et al., 1983; Sandrini et al 1987; ter Bruggen et al., 1990) and audiometry (Kuhn and Ey, 1966; Wright et al., 1988). Evidence for central involvement has come from studies employing brain-stem auditory-evoked potentials (BAEPs) (Thompson et al., 1983), SSEPs (Thompson et al., 1983; Bartel et al., 1984; Ganes and Kerty, 1988), VEPs (Sandrini et al., 1986) and electro-oculography (EOG) (von Noorden et al., 1964; Emre and Henn, 1985).

Evidence for a combination of peripheral and central abnormalities was found for the somatosensory system (Bartel et al., 1984) and the visual system (Sandrini et al., 1986). The present study was undertaken to find out whether the oculomotor, auditory and vestibular systems also exhibit a combination of peripheral and central dysfunctions in MyD patients, when studied with suitable methods.

PATIENTS AND METHODS

Our study population comprised 13 patients with MyD (see Table 1) (8 men and 5 women, aged 18–57 years, median age 39 years). The group included a father and two sons (Nrs. 12, 2 and 3) and a father and a daughter (Nrs. 11 and 1). All of the patients met the criteria for MyD according to Griggs and Woods (1989). General physical, neurologic and ophthalmologic examinations had been performed previously. Special attention was given to eye movement disturbances, muscle weakness, atrophy and myotonia. Visual acuity was measured. A slit lamp examination for lens opacities and funduscopy were performed. A routine otolaryngologic examination was performed on the day of testing. Examination results will be mentioned only where relevant. The assessment of the severity of MyD was based on both the Karnofsky index (Karnofsky and Burchenal, 1949) and the value of the MRC (Medical Research Council scale, 1943) sum score of 11 limb muscles (see Table 1).

Oculomotor system

Eye movements were recorded with d.c. EOG. The filter settings were 30 Hz low-pass for all the tests except for the saccade velocity test, for which 100 Hz was used. Calibration of eye movement was made before each test by having the patient look in alternation at two light dots 10° on either side of the primary position. The resulting (20°) saccades were analyzed as reported previously (Huygen, 1983), in this case using a 125 Hz sampling rate (both monocular horizontal leads) and an overall filter characteristic (from input to output including the numerical methods of smoothing and differentiation) with 3, 6, 12 and 18 dB points at 11, 15, 21 and 25 Hz, respectively. The primary saccades which had been best performed, i.e. were followed by only a small correction saccade if any, were selected for analysis; testing was continued until at least 4 representative saccades in each horizontal direction had been collected. Eyelid or other movement artefacts were avoided, if possible, by inspecting a vertical lead on the EOG and recorded close-up video pictures of the patient's eyes. The 5% lower confidence limit derived from measurements in 17 normal subjects (11 men, 6 women, aged 14–85 years) was 280°/s for the peak velocity; the upper 5% confidence limit for saccade duration was 100 ms. Smooth pursuit (SP) was tested using a light dot moving in a circular fashion[24] (radius 10°, peak velocities in horizontal and vertical directions 20°/s). Optokinetic nystagmus (OKN) responses were elicited with shadow stripes (7.5° width and separation), projected onto a hemicylindrical screen in front of the patient, which covered 100 × 50° of the visual field. The stimulus velocities used were 40 and 60°/s, the lower 5% confidence limit of response velocity was 20°/s. Gaze positions were tested to see whether there was any gaze nystagmus (in the light, the patient fixating a target at about 30° to 40° lateral displacement).

Auditory system

Pure tone audiograms (PTAs) were measured with an Interacoustics AC5 audiometer to determine the hearing threshold (in dB hearing level, HL measured according to ISO 8253[25]). We employed the method of ISO 7029 (1984) to calculate a P95 (95th percentile) threshold value for presbyacusis for each patient at each frequency, relating to the patient's age and sex. This method is almost equivalent to that of Robinson and Sutton (Robinson and Sutton, 1979) who presented a full account of this method. Only a hearing loss greater than the P95 value relating to presbyacusis will be called significant below. Tympanograms and contra- and ipsilateral acoustic middle-ear muscle reflexes were elicited and recorded with an Amplaid 720 tympanometer and x-y recorder.

BAEPs were obtained with a Medelec Sensor AS10/ER94a system linked to a PC. Silver-silverchloride cup electrodes were attached to the skin of the

forehead and both mastoids. The wrist served as the ground electrode. Skin potentials were amplified differentially with 20 or 50 μV input sensitivity and artefact rejection level. Filters were set at 100 Hz high-pass (cut-off 12 dB/octave down) and 6000 Hz low-pass (cut-off 6 dB/octave down). Monaural click stimuli (100 μs rectangular pulses) were delivered through Telephonics TDH-49P shielded earphones. The stimulus rate was 15 Hz; click intensity was 70, 80 or 90 dB HL. A masking white noise of 35, 45 or 55 dB HL intensity, respectively, was delivered to the contralateral ear. The final waveforms were obtained from either 2 × 2048, 4 × 2048 or 6 × 2048 (averaged) responses to stimuli of alternating polarity, which were sampled within a time window of 20 ms, using a 512 address memory. Time-related data pertaining to the component waves (for each click intensity) were tested on any abnormalities by applying 95% sex-related confidence limits which had been established with this equipment in our laboratory.

Vestibular system

Vestibular tests were conducted with the patient in the dark with the eyes open. It was checked whether there was any spontaneous nystagmus. Velocity step (VS) tests were performed with a Tönnies rotatory chair. After $0.8°/s^2$ acceleration and a period of 90°/s constant velocity long enough to let the perrotatory nystagmus response subside, the chair was stopped with $200°/s^2$ deceleration. The postrotatory nystagmus response was analysed with a computer method (Huygen, 1979, 1985; Theunissen et al., 1989), which utilized the parameter slow phase velocity (SPV) and yielded the following response parameters to characterize the vestibulo-ocular reflex (VOR): initial velocity (V, 90% confidence limits 30–65°/s), time constant (T, 11–26 s) and "Gesamt-amplitude" or cumulative eye displacement (G = VT, 485–1135°) (Theunissen et al. 1989).

Statistical tests

Individual values were compared to the above-mentioned normal values. Differences in the relative frequencies of any feature were tested in a 2 × 2 contingency table using Fisher's exact probability test; the F value (cf. P value) is specified only for significant differences (i.e. $F < 0.05$). Correlations between variables were analyzed after calculating correlation coefficients and first-order partial-correlation coefficients, provided the variables involved had (approximately) normal distributions and, in combination, showed linear and homogeneous bivariate relationships (as judged from scatterdiagrams). Correlations involving wave delay (BAEP) variables with their odd mixtures of zero and nonzero values (see Table 1) were evaluated by using Fisher's (distribution-free) exact probability test.

RESULTS

In general
All of the 13 patients showed abnormalities on at least one of the examinations. It was striking that 6 out of the 7 patients who were 39 years of age or older, i.e. the group of clinically generally more severely affected patients, showed one or more severe abnormalities, whereas none of the 6 younger patients showed such severe abnormalities. The difference is significant ($F = 0.020$) and provides evidence for increasing penetrance of abnormalities with increasing age. Part of the relevant patient data is shown in Table 1.

Oculomotor system

No gaze nystagmus was found in any of the patients. Two patients (Nrs. 11 and 13) had divergent strabism and convergence paralysis, one (Nr. 8) could not move his eyes by more than approximately 15° from the primary position. Limitation of convergence was found in 3 patients (Nrs. 1, 4 and 7). Other oculomotor abnormalities were not observed.

Saccades
Saccadic slowing was found in 10 out of the 13 patients and was moderate (peak velocity 225–270°/s) in 7 and severe (peak velocity 145–180°/s; duration 150–210 ms) in 3 patients. The latter 3 patients (Nrs. 8, 11 and 13 in Table 1) were among the oldest patients and those who showed the longest duration of disease (> 25 years) and were in the low ranges of both the Karnofsky index (60–70) and the MRC score (41–46). Interestingly, the 3 patients with normal saccades (Nrs. 9,10,12) were of about the same age as the patients with severe slowing but had a shorter duration of disease (< 25 years) and (most of them) higher clinical scores. It was remarkable that all of the patients who showed peak saccade velocities of below 265°/s had some type of clinically apparent limitation of eye movement: convergence paralysis with divergent strabism or limited excursion (Nrs. 8, 11 and 13) was linked to peak velocities in the range of 145–225°/s and limitation of convergence (Nrs. 1, 4 and 7) was linked to velocities in the range of 225–260°/s. Table 2 shows significant correlations of saccade peak velocity with duration of disease, Karnofsky index, MRC score and visual acuity. Partial-correlation analysis indicated that only the correlation with the Karnofsky index was resistant against controlling for any other relevant variable. The correlations with duration of disease and visual acuity are likely to be spurious, because they vanished when controlling for either of the clinical scores, which procedure attempts to "correct for" the patient's clinical condition.

OKN and SP responses
OKN responses were normal in all of the patients, both in horizontal and

Table 1

Nr.	age, sex, duration	Karnof index	MRC sum	vis. acuity	Sac. vel. (°/s)	SP	PTAs		BAEPs		VOR
							R 4–8 kHz (dB)	L 4–8 kHz (dB)	I–V IWD (ms)	I–III IWD (ms)	
1	18,F,11	80	46	1.0	**260**	n	n,0–0	n,0–0	n /.43*	n	n
2	20,M,3	80	52	1.0	**270**	n	n,**15**–10	n,**15**–10	.41/.40	n	↑
3	21,M,2	90	55	1.0	**270**	n	n,**15**–5	n,10–10	n	n	n
4	30,F,1	80	47	0.6	**250**	n	n,10–15	↓,**20–30**	n /.40	n /.33	↑
5	36,F,24	80	47	0.8	**265**	n	n,0–15	n,0–20	.39/.39	.33/ n	n
6	38,M,18	80	47	1.0	**270**	n	↓,20–**35**	↓,15–**35**	n	n	n
7	39,F,3	70	53	0.8	**225**	n	↓,**15–40**	↓,10–**30**	.45/.59	n	↑
8	39,M,26	70	46	0.6	**180**	n	↓,15–**35**	↓,**35–85**	n /.37	n	n
9	39,M,23	70	52	0.8	315	n	↓,25–**60**	↓,**35–55**	n	n	↓
10	42,F,3	80	54	0.9	315	n	↓,20–**40**	↓,20–**45**	.39/.35	n /.33	n
11	45,M,28	70	42	0.5	**225/180***		↓,10–**45**	↓,15–**60**	.54/.65	n	↓
12	45,M,10	90	50	0.9	340	n	n,**40**–20[d]	n **70**–40[d]	n /.70	n	n
13	57,M,37	60	41	0.3	**145**	↓	n,20–55	n 30–55	n	n	↓

*, On/towards the right and the left side, respectively ; n, normal; ↓, defective (SP) / significant hearing loss at 8kHz (PTA) / hyporeflexia (VOR); ↑, hyperreflexia (VOR); [a], Karnofsky scale; [b], MRC sum score – summation of the best score of the deltoid, biceps brachii, triceps brachii, flexor carpi radial, extensor digitorum, abductor pollicis, iliopsoas, quadriceps, triceps surae, anterior tibial and long peroneal muscles (maximum 55) (British Medical Research Counsil, 1943); [c], the visual acuity of the best eye is mentioned; [d], noise exposure.

Table 2. Correlation coefficients for the variables with normal distributions and linear homogeneous bivariate relationships

	Age	Duration	Karnofsky index	MRC score	Visual acuity	Saccade velocity	*PTA (8 kHz)*	
							Right	Left
Age	1							
Duration	**.63]}**	1						
Karnofsky index	**−.57 |]**	**−.69)|**	1					
MRC score	−.43	**−.82**	.54	1				
Visual acuity	**−.68 |]**	**−.75]}**	**.76 |**	**.71 |]**	1			
Peak velocity	−.31	**−.59)]}**	**.73**	**.68 |]**	**.75]|**	1		
PTA (8 kHz)								
Right	**.81**	**.56)]**	**−.76**	−.22	**−.57) |]**	− 28]	1	
Left	**.74**	**.62)]}**	**−.59) | }**	−.36	**−.66) |]**	−.38	**.77)**	1

Significant values (13 data points, r = ±.55 for P = 05) in **bold print**), Partial-correlation coefficient not significant when controlling for age; |, for duration,], for Karnofsky index;), for MRC score;], Partial-correlation coefficient significant when controlling for Karnofsky index

vertical directions. Smooth pursuit responses were normal in all the patients except for two (Nrs. 11,13) who showed many saccades but also occasional smooth hemicycles of sinusoidal response (cf. ref. 8). These two latter patients had the lowest visual acuity (0.3–0.5). They were the same as the two above-mentioned patients with divergent strabism and convergence paralysis.

Auditory system

PTAs

A significant sensorineural high-tone hearing loss, most prominent at 8 kHz (30–85 dB, see Table 1) was found in 7 patients (Nrs. 4,6–11). All of these cases showed descending audiometer curves beginning at 1 kHz or 2 kHz, their hearing loss becoming prominent only at the highest frequencies and leaving the speech frequencies almost unaffected. A significant hearing loss at 4 kHz is indicated in Table 1 for 3 additional patients (Nrs. 2, 3 and 12). In patient Nr. 3, the maximum hearing loss was found at 2 kHz (20–25 dB) bilaterally. Patient Nr. 2 had a significant bilateral loss (15 dB) only at 4 kHz. Patient Nr. 12 had a most prominent loss at 4 kHz bilaterally which was ascribed to heavy noise exposure. We did not attribute the hearing loss observed in patients Nrs. 2, 3 and 12 to MyD. The (significant) hearing loss at 8 kHz was bilateral and symmetrical within 20 dB in most cases. In one case (Nr. 4) it was unilateral and in another case (Nr. 8) there was a difference of 50 dB between left and right. In the younger age group (< 39 years), 33% (2 out of 6) of the patients showed a substantial hearing loss (at 8 kHz) as opposed to

71% (5 out of 7) in the older age group (39 years and older); the difference is not significant. The (significant) hearing loss, however, was more severe in the older age group (30–85 dB at 8 KHz) than in the younger age group (30–35 dB at 8 kHz).

Table 2 shows significant correlations of high-tone hearing loss with age, duration of disease, Karnofsky index and visual acuity. Only the correlation with age was resistant against a partial-correlation analysis. The other correlations are likely to be spurious, perhaps except for the one with the Karnowsky index, i.e. for one side only.

Tympanometry and acoustic reflexes

Normal tympanic membrane mobility was found in all of the 11 patients measured (assessment had been omitted in Nrs. 2 and 3) except for one (Nr. 12) in whom mobility was bilaterally reduced, so we could not measure his acoustic reflexes. The reflexes were normal in all the other patients measured.

BAEPs

Some absolute wave delay of the total I–V complex was found in 4 of the patients (Nrs. 6,7,8 and 11) with a significant high-tone hearing loss at 8 kHz (range 0.1–0.38 ms), which was attributed to their hearing loss. It was also found in 5 patients (Nrs. 1,2,5,12 and 13) without such a hearing loss (range 0.09–0.19 ms). This type of delay will not be further considered below. A significant interwave delay (IWD) was found in 9 patients (Nrs. 1,2,4,5,7,8, 10–12, see Table 1). Such a delay was found in the I–V interval alone in 6 cases and in both the I–V and the I–III intervals in 3 cases.

All of the 5 women and 4 out of the 8 men had abnormal I–V IWD; the difference is not significant. Four patients (Nrs. 1,4,8 and 12) had a unilateral I–V IWD; this was associated with a significant hearing loss at 8 kHz in 3 of them, which was only present or most prominent on the same side in 2 of these patients (Nrs. 4,8), the third (Nr. 1) showed normal hearing on both sides. Only one patient (Nr. 3), who had the shortest duration of disease (2 years), had both normal PTAs at 8 kHz and normal BAEPs. The three other patients with a similar short duration (3 years) (Nrs. 2, 7 and 10) all showed bilateral IWD; the two oldest also had significant hearing loss at 8 kHz. Three patients (Nrs. 6,9,13) had normal BAEPs with bilateral high-tone hearing loss; in one of them (Nr. 13), the hearing loss could be ascribed to presbyacusis. All of the 5 patients (Nrs. 2,5,7,10,11) with bilateral significant I–V IWD had a significant bilateral high-tone hearing loss, except for the two youngest of these (Nrs. 2 and 5) who had a significant IWD (I–V) but normal PTAs at 8 kHz (for their age). For the patient group as a whole, IWD findings were not correlated with PTA findings. The BAEP findings were not clearly correlated with age: both normal and abnormal results were obtained from patients of various ages; the greater IWDs, however, tended to occur at a higher age. There was no significant correlation between the BAEP findings and the duration of disease, or the clinical scores.

Vestibular system

None of the patients showed spontaneous nystagmus (eyes open in the dark). An abnormal VOR was found in 6 patients. Three patients (Nrs. 2,4,7) showed hyperreflexia characterized by a significantly high gain (V, 68–79°/s; G, 1166–1420°). One of them (Nr. 2) had a mild chronic bronchitis. Patient Nr. 10 had a similar bronchitis but a normal VOR.

Hyporeflexia in both nystagmus directions characterized by a significantly short VOR time constant (T 4–9 s) was found in 3 patients (Nrs. 9, 11, 13). In each of these patients, the short time constants were associated with a high-tone hearing loss (45–60 dB at 8 kHz), although in one of them (Nr. 13) the hearing loss was not significantly higher than the upper confidence limit for his age (57 years). A significant IWD (0.54–0.65 ms) was found in only one case (Nr. 11). Two of these patients (Nrs. 11, 13) had severe saccadic slowing.

DISCUSSION

Oculomotor system

Saccades

The high incidence of saccadic slowing (77%) agrees with the 86% reported by Oohira et al. (1985) and the 83% recently reported in a different group of patients by Ter Bruggen et al. (1990), who used slightly different methods. The latter authors found severe slowing in 2 out of 18 patients evaluated with EOG. With the introduction of the saccade velocity test, Baloh et al. (1975) described 3 patients with MyD who showed severe slowing. We found only a slight reduction in peak velocity in 7 patients (54%), whereas in the report by Ter Bruggen et al. (1990) 72% was indicated. Just as in the latter report, we found that saccadic slowing can be detected in MD patients of any age. It must be emphasized that slowing was apparent on visual inspection only in the 3 most severe cases. The present study therefore confirms the previous observation that a moderate reduction in saccade peak velocity is an important subclinical finding in MyD. The present 3 cases with the most severe saccadic slowing were found among the older, more severely affected patients, just as the 2 cases previously reported on by Ter Bruggen et al. (1990). All of the 6 patients with the slowest saccades (peak velocities in the range of 145–260°/s) had some type of clinically apparent limitation of eye movement (it should be noted that the saccade test covered excursions of only ±10° from the primary position, which all of the patients were able to perform). No eye movement abnormality whatsoever had been apparent upon visual inspection in the other 4 cases with significant saccadic slowing (peak velocities in the range of 265–270°/s). So it may be that limitation of eye movement is an indication of (more severe) saccadic slowing, but it is also clear that (moderate) saccadic slowing was a subclinical finding in at least 4 of the cases.

Saccade peak velocity correlated significantly with the clinical scores (especially the Karnofsky index). Presumably, this has caused a spurious correlation with visual acuity because the latter variable also correlated with the clinical scores. The fact that reduced visual acuity and reduced peak velocity tended to co-exist in the clinically more severe cases accounted for the significant correlation. The observation that the correlation vanishes when controlling for the effects of the clinical condition, indicates that a causal relationship is unlikely (this also applies to the above-stipulated correlation between high-tone hearing loss and visual acuity, which we included as a more obvious example of a spurious correlation). In a current study on patients with Usher's syndrome, who also have reduced visual acuity, we did not find any saccadic slowing sofar (n = 29).

Two possible explanations might apply to the phenomenon of saccadic slowing in MyD. One is based on a dysfunction on the central (pre)motor level and the other on a dysfunction on the level of the extra-ocular muscles. Emre and Henn (1985) have argued that a peripheral mechanism cannot offer an explanation for the dissociation between rapid and slow eye movements or the dissociation they observed between horizontal and vertical saccades. They consider the rostral pole of the paramedian pontine reticular formation (PPRF) to be a likely candidate for a bilateral lesion which might explain such types of dissociation. Ter Bruggen et al. (1990) favour a peripheral (myopathic) pathophysiologic mechanism. They suggest a selective abnormality of the peripheral large muscle fibres with "en placque" nerve endings (labelled as "granular" and "fine" based on histochemic features) which show a fast (twitch) activity as required for saccades. This would be combined with the relative preservation of the small muscle fibres (with a "coarse" microscopic aspect) with "en grappe" nerve endings, which show more tonic activity, as is required for smooth pursuit and the slow phase of nystagmus (Ringel et al., 1978).

It would appear that a selective abnormality of phasic extra-ocular muscle activity would result in a pulse-step mismatch of a peripheral nature. If this is so, why did we not observe any sign of such a mismatch, i.e. a hypometric saccade followed by a postsaccadic drift (called "glissade" by Weber and Daroff (1972) "from the position initially given by an inadequate pulse to the gaze angle specified by the step" (Abel et al., 1978). Presumably, such a mismatch – by analogy with peripheral abducens (Kommerell et al., 1976) or oculomotor nerve weakness (Abel et al., 1978) – can be overcome by a central plastic adaptation of the pulse of saccadic innervation. Abel et al. (1978) showed that the adaptive adjustment of saccadic amplitude depended on changing saccade duration. Optican et al. (1982) could also correlate adaptive changes in saccadic innervation to abnormal extra-ocular muscle forces. Given the observation that during a normal saccade, the antagonist relaxes completely (Robinson, 1975) and that it is in the nature of MyD that relaxation can be impaired by myotonia, as was also demonstrated in extra-ocular muscles (Davidson 1961; Lessel et al., 1971; Oohira et al., 1985; ter Bruggen et

al., 1990) it may well be that abnormal muscle forces are involved. Such abnormal forces could be the cause of initially undershooting saccades and the ensuing adaptive changes in saccadic innervation, if they occur, might consist of an increase in the height of the saccadic pulse – as much as possible – and an increase in the duration of the saccadic pulse which, despite the decrease in velocity (due to peripheral restraining muscle forces), takes the eye to the intended gaze angle.

OKN and SP responses

OKN responses were normal in all of the patients, including the two who showed many saccades in their SP response. We are therefore inclined to attribute the poor SP response to their poor visual acuity (0.3–0.5); remarkably, they also had convergence paralysis and divergent strabism. Normal SP responses have also been reported by others (Junge, 1966; Oohira et al., 1985; ter Bruggen et al., 1990). Contrary to this, the report by Von Noorden et al. (1964) stated that horizontal SP responses were defective in all of their 10 patients with MyD. It appears to us, however, that in at least one of their recordings, depicted in their figure 8, which they called "a representative sample for the entire group", some smooth parts of the response can be found at each of the frequencies (peak velocities 20–45°/s). In view of the fact that most patients with MD have reduced vision due to cataract and retinal abnormalities (Miller, 1985; Burian and Burns, 1967), we would not be inclined to accept a deficit in visual following responses, unless it showed up in both the SP and the OKN responses. OKN responses were not reported on by Von Noorden et al. (1964). The only previously published OKN responses in MyD concerned one patient reported on by Emre and Henn (1985). His horizontal eye movement responses were not calibrated, because he could not perform any horizontal saccades but, nevertheless, he showed the presence of SP and OKN responses. The latter were more lively in vertical directions, where he had preservation of saccades. The findings suggest that the horizontal OKN gain was too low. The horizontal SP response looked fairly smooth, but we cannot infer the absence of saccades from that observation, because the horizontal saccades were so severely impaired.

Auditory system

PTAs

The present findings were very similar to those reported previously by Kuhn and Ey (1966). The effect of age was also similar, but in our smaller sample we found no significant increase in the number of individuals showing a significant hearing loss at a higher age. However, the hearing loss (at 8 kHz) was most severe in the older age group and the correlation with age was significant (and did not vanish by partialing out any relevant variable). We did not find, nor did Kuhn and Ey (1966), any major involvement of the

speech frequencies such as that reported by Wright et al. (1988). In view of the total wave delay (of the I–V complex) found in the BAEPs in some of the present cases, or even the presence of fully normal BAEPs in others, we have no other explanation for the high-tone hearing loss than involvement of the cochlea and/or the cochlear nerve. There was some indication of a significant correlation between high-tone hearing loss and the Karnofsky index, however, the significance was lost for the left side after partialing out age, duration or MRC score.

Tympanometry and acoustic reflexes

We found only one case with reduced tympanic membrane mobility, whereas Wright et al. (1988) reported abnormal mobility in 8 out of their 25 cases. In the report by Kuhn and Ey (1966) the suggestion can be found that in MyD the cochlea might be more vulnerable to damage caused by noise exposure. We cannot exclude that possibility, but our demonstration of normal acoustic reflexes at least shows that such an effect, if it exists, cannot be due to a defect in that noise-protection mechanism.

BAEPs

The proportion of our patients with BAEPs showing significant IWD (69%) was higher than that reported by Thompson et al. (1983), i.e. 53%. The IWD findings themselves were fairly similar, although we did not find cases with isolated I–III IWD, as reported by the latter authors. Wright et al. (1988) had difficulty in evaluating IWD in 2 cases caused by a predominant influence of a major peripheral hearing loss; they found normal values in 2 patients and a bilaterally delayed wave V in one. Just as Thompson et al., 1983, we had no special problems related to peripheral hearing loss and attributed the total wave delay found in a number of patients to the high-tone cochlear loss shown in the PTAs. In some patients with significant high-tone hearing loss, it even appeared that their BAEPs were completely normal. In the patient group with IWD reported on by Thompson et al.(1983), there was a significantly low number of women. In our group, all of the 5 women had IWD and only 4 out of the 8 men.

The IWD, which was also present in some of our patients with normal PTAs and, more in general, was not correlated with PTA findings, can only be interpreted in favour of a central, i.e. brain stem (auditory) dysfunction. Other studies have also indicated central conduction abnormalities of other evoked potentials in MyD, such as median nerve SSEPs (Thompson et al., 1983; Bartel et al., 1984; Ganes and Kerty, 1988) and pattern VEPs (Gott et al., 1983; Sandrini et al., 1986; Ganes and Kerty, 1988; Pinto et al., 1987; ter Bruggen et al., 1990). The present study did not indicate any useful correlation between BAEP findings and clinical scores.

Vestibular system

It is tempting to speculate about the finding of vestibular hyperreflexia in MyD, because, in principle, this is a central abnormality, which has been reported in vestibulo-cerebellar dysfunction (Baloh et al., 1975), multiple sclerosis (Huygen, 1983), the hyperventilation syndrome (Theunissen et al., 1986) and idiopathic spasmodic torticollis (Huygen et al., 1989). It can be suggested, for example, as in the latter report, that patients with MyD have limited head movements and, therefore, develop an enhanced VOR. First, however, it must be concluded that in the present series the relative frequency of hyperreflexia is not significantly higher than could have been expected on the basis of false positivity (see ref. 31 for a statistical discussion). Second, one of our patients also had mild chronic bronchitis and our clinical experience indicates that such patients fairly often show vestibular hyperreflexia.

The feature of vestibular hyporeflexia with short time constants was not found in a significant number of patients in our study, either, but nevertheless it merits special attention. The first patient (Nr. 9) with vestibular hyporeflexia had a pronounced bilateral high-tone hearing loss and completely normal BAEPs (even without a total wave delay). A labyrinthine deficit which involves both the cochlear and the vestibular parts, is a possible explanation. Such a possibility cannot be excluded in the second patient with hyporeflexia (Nr. 11), who also had a significant bilateral high-tone hearing loss and IWD but, in addition, had severe saccadic slowing. However, the former two abnormalities often came together in the present group of patients, whereas vestibular hyporeflexia occurred only in a minority. The third patient with hyporeflexia (Nr. 13) had a high-tone hearing loss which was not abnormal for his age, normal BAEPs and also severe saccadic slowing. In the second and the third patients, there are two possible explanations for their hyporeflexia: a dysfunction of the semicircular canals or the ampullary nerves, or a central deficit. In the latter case, similar to our previously reported findings on multiple sclerosis, it might be that the hyporeflexia is associated with, or secondary to, a central oculomotor dysfunction of, for example, the saccadic system (Huygen et al., 1990). It can be shown that the latter two (among the 3 oldest, i.e. age 45–57 years) patients combined two relatively infrequent features, i.e. vestibular hyporeflexia ($P = 3/13$) and severe saccadic slowing ($P = 3/13$). The number of cases which can be expected to have this specific combination in a sample of size 3 is: $3(3/13)(3/13) = 0.16$; according to Poisson tables, a frequency of 2 is significant ($P = 0.012$). This implies that it might not be a coincidental finding that 2 out of the 3 oldest patients (with the longest duration of disease) had developed a clinical picture which combined vestibular hyporeflexia with severe saccadic slowing. If these two abnormal features are indeed linked, we may assume, by analogy with multiple sclerosis (Huygen et al., 1990), that they share a common central causative factor. Another calculation showed that the combination of several abnormalities might also be associated with an increase of penetrance with age. If we take

the chance for each abnormality in the older age group from a lower limit at 39 years, which is the youngest age at which any of these abnormalities was found, the number of cases that can be expected to have both abnormalities is $7(3/7)(3/7) = 1.29$, thus a frequency of 2 is not significant ($P = 0.37$).

In summary, it is clear that with application of the above-mentioned tests, (subclinical) peripheral and/or central disturbances of the oculomotor, auditory and vestibular systems can be detected in MyD patients.

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STATISTICAL REVIEW

P.L.M. Huygen is a biostatistician/physiologist.

CHAPTER 4.1

MYOTONIC DYSTROPHY: FUNCTIONAL BEDSIDE VALIDATION OF SILENT DYSPHAGIA

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(submitted)

INTRODUCTION

Myotonic dystrophy (MyD) has the highest overall prevalence and incidence of inherited muscular dystrophies in the general population of Western Europe (incidence: 1/8000) (Emery, 1991). Upper gastrointestinal (GI) motility disturbances are frequent (up to 80%) and cause considerable morbidity (Eckhart et al., 1986; Harper, 1989). Pharyngeal peristalsis has been reported to be of low amplitude with diminished upper oesophageal pressure and normal sphincter relaxation (Swick et al., 1981; Eckhart et al., 1986). Gastric emptying (Horowitz et al., 1987a,b) and small intestine motility may be also disturbed (Nowak et al., 1984). This may lead to delayed oesophageal emptying for solids and liquids (Eckhart et al., 1986; Horowitz et al., 1987a,b). The basic mechanism of dysphagia is a combination of myotonia (Bosma and Brodie, 1969) and weakness of the striated and smooth muscles (Eckhart et al., 1986). The influence of the latter is of minor importance for dysphagia (Eckhart et al., 1986).

Sudden aspiration followed by pneumonia is a hazardous complication of MyD, which may occur anywhere in the progressive course of the disease (Harper, 1989). A correlation between GI symptoms and severity of limb muscle weakness is lacking (Swick et al., 1981; Horowitz et al., 1987a). Therefore, there remains a need to identify and follow patients who are at greatest risk for dysphagia or aspiration and thus in need of extensive studies of swallowing function.

PATIENTS AND METHODS

Patients

Twenty-six MyD patients and 28 age matched healthy volunteers were investigated according a standard protocol. Only cooperative patients with the 'classical' (adult onset) form of MyD without prominent mental dysfunction or severe proximal weakness were included.

Methods

A standardized questionnaire for swallowing (Horowitz et al., 1987a), a bulbar rating scale (BRS, Appel et al., 1987) and a slightly modified (150 cc versus 50 or 90 cc) quantitative swallowing test (ST) were used in all individuals (Gordon et al., 1987; DePipo et al., 1992). Patients were asked to drink 150 cc (5-oz) water from a cup without interruption (standard teacup; 20 degr.C.). The duration to empty the cup was measured with a handhold stopwatch. All tests were performed twice by two separate investigators and the shortest time was noted. Coughing within 1 minute after swallowing or a postswallow wet-hoarse voice quality were regarded as signs of aspiration. ST was defined abnormal if its value exceeds the mean and two times the standard deviation of the controls. The severity of muscular symptoms was graded according to

an international rating scale for MyD reported by Mathieu (1992): grade I means clinically asymptomatic but characteristic changes on EMG or typical lens crystals, grade II minimal distal limb involvement, grade III moderate distal limb involvement, grade IV proximal weakness as well and grade V wheelchair-bound or severe proximal weakness. Due to the fact that in MyD (peri)oral weakness coexists with pharyngeal dysfunction (Harper, 1989), we measured the perioral function in order to prevent false positive results for swallowing function. In this instance we used the 'snout-index' (Jansen et al., 1990): perioral weakness was expressed as the procentual decrease from the intercommisural distance (ICD) in rest and after repeated 'snouting', measured after a warming up to prevent myotonia (Jansen et al., 1990). The quotient of perioral function (mean Snout-index) of MyD patients and controls may act as a factor for the influence of the (peri)oral phase.

Statistical analysis
SAS and CIA statistic computer-programs were used. For correlations, Pearsson's correlation coefficient and for group differences, Wilcoxon unpaired ranksum test were chosen.

RESULTS

The major results are summarized in table 1. The group of MyD patients counted 9 females and 17 males (mean age: 35 yrs, SD: 8.7), while the control group had 11 females and 17 males (mean age 32 yrs, SD: 7). Only 3 patients were aware of mild swallowing difficulties. Using the questionnaire 4 more patients revealed mild dysphagia complaints. The duration of swallowing was significantly prolonged in 65% of the MyD patients (17/26, see fig. 1). Furthermore the values of mean ST were significantly different between MyD patient group and the controls (Wilcoxon, $p < 0.01$).

Perioral weakness was of minor importance for the duration of ST. This has to be concluded by a persistent differences of the mean ST duration before and after correction for perioral weakness (see methods) (Wilcoxon, $p < 0.01$).

The duration of swallowing is related to the severity of the weakness of the limb muscles. Two arguments support this. First, the ST duration (R: 0.44) correlates with the Mathieu score, which expresses the severity of limb muscle involvement ($p < 0.05$, Wilcoxon). Secondly, the ST duration increases significantly (Wilcoxon, $p < 0.05$) from nearly asymptomatic patients (Mathieu I) to severely involved patients (Mathieu IV) (differences of the means: −4.6 (95%CI: −7.8 to −1.36).

The results of the questionnaire are unrelated to the ST results, although the mean ST (10.8, SD: 1.8) for 7 patients with swallowing difficulties but without aspiration showed a trend to be prolonged. The test is rather safe, finding only once signs of aspiration in a patient with an extremely prolonged ST: 21 sec.

Table 1. *Results of clinical investigations*

		MyD patients		controls
number		26		28
Mathieu score	I	5		–
	II	4		–
	III	12		–
	IV	5		–
swall. complaints#		7/26	NS	0
BRS abnormal		4/26	NS	0
ST abnormal		17/26	**	0
Mean ST: Mathieu	I	**8.7*** SD 2.9	**	4.6 SD 1.8
	II	10.0 SD 4.7		
	III	11.4 SD 4.4		
	IV	**13.3*** SD 1.2		
Snout abnormal		16/26	**	1/28
Mean 'Snout' (SD)		20.5% SD 8.0	**	32% SD 6.0

M I–IV:	Mathieu score, indicating a rating scale for limb muscle involvement
#:	dysphagia according questionnaire
BRS:	bulbar rating scale (Apple, 1985)
ST.	investigated swallowing test
Mean ST M.II/III/IV:	ST results Mathieu II vs III vs IV
**.	$P < 0.01$ (Wilcoxon ranksum test)
*:	$0.01 < P < 0.05$
NS·	not significant
Snout:	parameter for perioral dysfunction

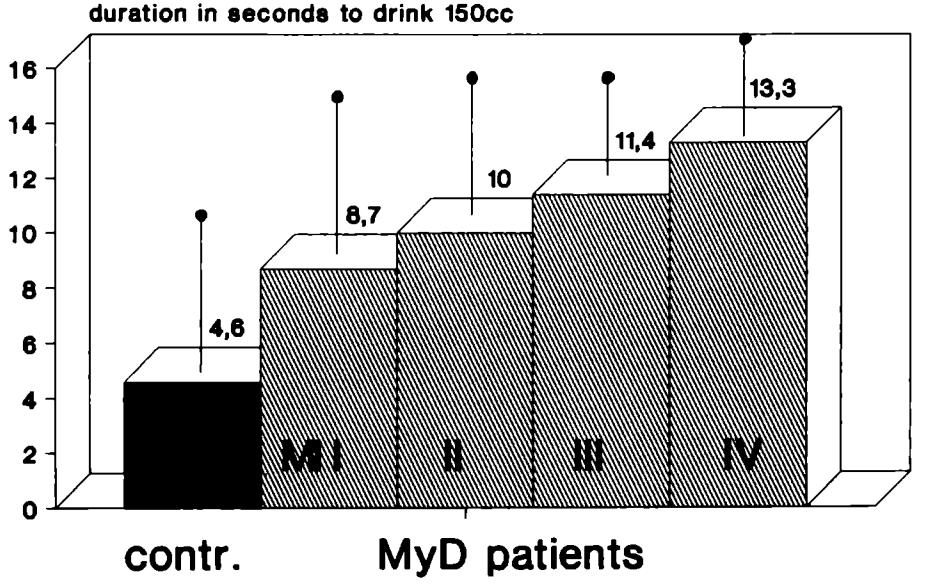

Fig. 1. *Graphical presentation of the mean duration of swallowing (ST) in patients with myotonic dystrophy and controls. M I–IV refers to a neuromuscular disability rating-scale specific for MyD patients, developed by Mathieu et al (1992).*

DISCUSSION

Our observations show that even in minimal and moderate phases of adult onset MyD the duration of swallowing, measured by the ST test is prolonged. This causes only in a minority swallowing difficulties and seldom aspiration.

In agreement with previous reports (Jerusalem et al., 1985; Cook and Glass, 1987; Gordon et al., 1987; DePipo et al., 1992), ST acts as an assessment for dysphagia. Although one must assume some co-influence of (peri)oral weakness in MyD besides pharyngeal/oesophageal dysfunction, this alone cannot completely explain the current ST findings. For MyD, ST mainly depends on swallowing function, however the current test does not discriminate between oral, pharyngeal and oesophageal phases.

What is the value of screening for swallowing with a bedside test like ST in MyD? Firstly, a severely prolonged duration of ST (duration > 14 seconds) justifies more extensive gastro-intestinal investigations. Further studies are required to assess at what duration of ST, aspiration may occur. Secondly, repeated measurements may monitor the natural history of swallowing difficulties and document the increase of dysphagia of an index patient.

The current swallowing test (ST) bears some advantages. First of all it is a wellknown quantitative test, able to reflect minor changes. The used ST is easy and safe to perform, nearly without side effects: only in 1 of 26 patients (4%) aspiration was noticed. In addition the test was found rather discriminative from healthy controls (sensitivity: 0.65; specificity: 0.75) for a functional test in a minimally and moderately affected group. Although experience is mainly gathered for motor neuron diseases (Jerusalem et al., 1985), Guillain Barré syndrome (Cook and Glass, 1987) and cerebro-vascular diseases (Gordon et al., 1987; DePipo et al., 1992), this study revealed its usefulness in a slowly progressive disorder like MyD as well.

For cerebrovascular events DePipo (1992) used a similar test with 90 ml of water (with videofluoroscopic barium swallow examination as golden standard) and found a sensitivity to predict aspiration in 76–94% with false negative results in 10%. The specificity to predict aspiration was rather low: 26–30% in the former study. False positive results were due to other coexisting oral or pharyngeal swallowing abnormalities. In our study we tried to minimalize this by using a correction factor for (peri)oral weakness.

To summarize, in accordance with previous reports (Swick et al., 1981; Horowitz et al., 1987a,b) we confirm that upper pharyngeal motor dysfunction in MyD is highly variable and may occur in absence of swallowing complaints. In contrast to the former reports, but rather in agreement with clinical experience, this is the first study to suggest that swallowing dysfunction probably gets worse during the successive phases of MyD. Because MyD is highly variable, a true progression in previous swallowing studies may be discarded. By selection of only the adult onset group of MyD patients and using a quantitative method we are able to explain this point of controversy. In this study as well, other options for severity of dysphagia like question-

naires or rating scales are insufficient for follow up (Horowitz et al., 1987a). Furthermore, our study demonstrates that the ST is sensitive enough to monitor the course or to be used as screening tool for further swallowing examination. Future studies are suggested to evaluate the merits of ST as a bedside screening tool for identifying MyD patients at risk for aspiration. How long is the ST in MyD patients with clinical signs of dysphagia or first time aspiration and what is the correlation with definitely abnormal Barium studies? Is there any influence of posture on this type of functional swallowing testing? At last, how powerful is the current ST to monitor medical inventions?

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CHAPTER 4.2

QUANTITATIVE ASSESSMENT OF SPEECH-MOTOR PROGRAMMING AND EXECUTION IN MILDLY AFFECTED, EARLY-ADULT AND ADULT MYOTONIC DYSTROPHY

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INTRODUCTION

Myotonic dystrophy (MyD) is an autosomal dominantly inherited multisystem disease, which is characterized by progressive muscular weakness, atrophy and myotonia. Facial-bulbar muscle weakness is characteristic for adult-onset MyD, which can result in a peripheral disorder of speech-motor execution, in particular flaccid dysarthria [Darley et al., 1975]. The available clinical descriptions of speech in MyD patients [Weinberg et al., 1968; Griggs et al., 1989] are *qualitative* and therefore insufficient to assess a possible concomitant: a more central disorder of speech-motor programming – apraxia of speech.

In the present study we selected mildly affected, early-adult and adult onset MyD-patients. The patients had no intellectual impairment and no known neuropsychological dysfunction. The question was: Given the fact that there is muscular involvement, to what extent does this affect the speech-motor function? If only dysarthric signs are observed, this suggests that the disease is restricted to speech-motor execution. If apraxic signs are also observed, this is evidence for the additional involvement of speech-motor programming.

In order to determine whether MyD speech contains apraxic characteristics and to specify the type of dysarthria further, a set of speech- and oral-motor tasks was administered to assess the integrity of speech-motor programming and speech-motor execution on a quantitative level.

SUBJECTS AND METHODS

Subjects

The experimental group consisted of 15 patients with early-adult and adult onset MyD. The patients were asked to participate during a consultation at the Department of Neurology, University Hospital Nijmegen. The following selection criteria were applied. The patients were members of kindreds with classical myotonic dystrophy in accordance with the published criteria [Griggs et al., 1989], and were classified as adult or early adult onset with a mild or moderate severity of neuromuscular disability [Harper, 1989]. The diagnosis of MyD was made by DNA linkage analysis in their families [Brunner et al, 1989a], and positive (myotonic) EMG and/or split-lamp test [Griggs et al., 1989; Brunner et al., 1989a]. Other inclusion criteria were: Muscular Disability Rating Scale score of 3 or less [Mathieu et al., 1992]; and normal hearing. The patients had no intellectual impairment according to anamnestic information; this was confirmed by neuropsychological assessment (mean IQ: 107.6). The group consisted of 8 female and 7 male subjects with a mean age of 36.2 years (sd=8.6 yrs.). The duration of the disease ranged from 0;3 years (0 years, 3 months) to 30;0 years with a mean of 11;0 years (sd=8;4 yrs.).

For each MyD subject, a control subject was selected and matched with respect to age, sex and educational level. The control subjects reported a history free of speech- or hearing-related problems. Informed consent was

Table 1. Subject characteristics of the experimental (MyD) and the control group

Exp. Gr. (MyD)				Severity					Control Group			
	Age	S	El	Inh	Dur	MDRS	SI	M		Age	S	El
1	27	F	2	P	13,0	3	23	Y	16	27	F	2
2	30	F	1	P	14,0	3	14	N	17	30	F	1
3	36	F	3	P	21,1	3	16	Y	18	36	F	3
4	22	F	1	M	2,8	3	33	Y	19	23	F	1
5	38	F	3	M	5,0	3	18	Y	20	38	F	3
6	42	F	1	M	5,0	3	–	Y	21	43	F	1
7	49	F	1	P	10,0	2	–	Y	22	40	F	1
8	52	F	1	M	7,0	2	–	Y	23	57	F	1
9	26	M	2	P	5,6	3	–	Y	24	26	M	2
10	28	M	2	M	0,3	2	15	N	25	31	M	2
11	32	M	3	P	6,6	3	15	Y	26	31	M	3
12	32	M	3	P	10,0	3	–	Y	27	34	M	3
13	37	M	3	P	18,11	3	12	Y	28	38	M	3
14	41	M	2	M	30,0	2	28	Y	29	35	M	2
15	43	M	1	M	18,0	3	–	Y	30	40	M	1

Note S sex F=female, M=male
El Educational level 1=lower, 2=intermediate, 3=higher education
Inh inheritance P=paternal, M=maternal
Dur duration in years,months
MDRS Muscular Disability Rating Scale [Mathieu et al, 1992]
SI snout index (perioral weakness indicator [Jansen et al, 1990])
M myotonic EMG limbs (Y = positive, N = negative)

obtained from both the experimental and control subjects. In Table 1 the subject characteristics are summarized.

In a brief interview at the beginning of the speech-motor assessment session, eight of the experimental group patients reported initiation problems in their speech, which were reported to disappear after motoric warming-up. In three patients reduced intelligibility and increased speech exertion were reported as the first signs of fatigue. No effects of psychological condition, other than fatigue, were reported.

To obtain an initial characterization of the subjects' speech, the interviewing speech pathologist evaluated fragments of spontaneous speech produced during the interview. The speech of ten patients was judged as unremarkable. Five patients showed slight signs of imprecise articulation. Overall, the patients were perfectly intelligible and the speech signs were judged to be mild.

Procedure

The patients were administered a neurological examination and a number of speech and oral motor tasks. Two of the speech and oral motor tasks were intended to assess integrity of motor execution and two of the tasks were intended to assess motor programming. Maximum Sound Prolongation and Maximum Repetition Rate for monosyllabic sequences were used to measure motor execution or dysarthria Maximum Repetition Rate of multisyllabic

sequences and Pseudoword Imitation were used to measure motor programming or apraxia of speech.

For the *Maximum Sound Prolongation* task, the subjects were requested to sustain the speech sounds /a/, /z/, /s/, and /f/ for as long as possible. After instruction they were given three trials and the best of these was used for analysis. Performance on the Maximum Sound Prolongation task depends on the respiratory mechanism and on the integrity of the phonatory and articulatory mechanisms [Kent et al., 1987; Wit et al., 1993]. Thus, prolongation differences between the voiced /a, z/ and voiceless /s, f/ sounds, – and the s/z ratio in particular – are of diagnostic significance for laryngeal problems [Eckel and Boone , 1981; Mueller et al., 1991]. Prolongation of /f/ predominantly tests the lips, and prolongation of /z, s/ predominantly test the tongue tip [Kent et al., 1987; wit et al., 1993].

For the *Maximum Repetition Rate of monosyllabic sequences* the subjects were asked to repeat the following sequences as fast as possible: "papa.." (phonetic notation: /pApA/) and "fafa.." (/fAfA/) to test the lips and the jaw; "tata.." (/tAtA/) and "sasa.." (/sAsA/) to test the tongue tip; and "kaka.." (/kAkA/) and "xaxa.." (/xAxA/) to test the tongue body. The subjects were given several trials, and the best of these was selected for analysis. A reduced repetition rate in monosyllabic sequences points to motor *execution* problems and has been found to characterize several types of dysarthria [Fletcher, 1972; Darley et al., 1975; Kent and Rosenbeck, 1982; Wit et al., 1993; Wit et al., in press]. Such reduced repetition has not been found to characterize apraxia of speech [Kent and Rosenbeck, 1982].

For the *Maximum Repetition Rate of multisyllabic sequences* the subjects were asked to repeat the sequences "patakapataka.." and "fasaxafasaxa.." as fast as possible. A reduced repetition rate in multisyllabic sequences relative to the monosyllabic sequences is often used as a criterion for the selection of apraxic subjects [Aram and Horowitz, 1983; Dewey et al., 1988] and points to a motor *programming* dysfunction.

The *Pseudoword Imitation* task consisted of 27 pseudowords. The successive consonants within each pseudoword were highly similar, which is known to elicit speech errors in subjects with apraxia of speech [Thoonen and Maasen, 1992; Maasen and Thoonen, 1993].

Data Analysis

Acoustic analysis. To obtain a Maximum Sound Prolongation score, the durations of the three trials per sound were measured directly from the audiotape using a stopwatch. After selection of the longest trial, this trial was then measured twice again. The total Maximum Sound Prolongation was calculated by averaging the mean durations for the /a/, /z/, /s/, and /f/ sounds.

The Maximum Repetition Rate of monosyllabic sequences was measured in a semi-automatic way using a digitized signal. Syllable durations and consonant durations were determined according to the procedure of Ziegler et al. [1988]. In addition, a consonant ratio was calculated by dividing the

duration of the consonant by the total syllable duration.

The multisyllabic sequences "pataka.." and "fasaxa.." were analyzed more globally: The total duration of the utterance was divided by the number of syllables.

Pseudoword imitations were phonetically transcribed and analyzed with the LIPP phonetic analysis software [LIPP, 1991]. The following calculations were then made: (1) the frequency and percentage of substitutions; (2) the frequency and percentage of omissions; and (3) the percentage retention for place-of-articulation, manner-of-articulation, and voicing [Klich et al., 1979; Maasen et al., 1991; Maasen and Thoonen, 1993].

Statistical analysis. Analyses of variance were performed on the MSP and MRR measurements. Factors in the analysis were: Group (MyD, Control subjects), Sound (/a/, /z/, /s/, /f/), and for the monosyllabic sequences: Place-of-articulation (labial: /p, f/, alveolar: /t, s/ and velar: /k, x/), and Manner-of-articulation (Plosive: /p, t, k/, Fricative: /f, s, x/ sequences). The multisyllabic durations were analyzed separately against the mean monosyllabic durations. All effects were tested against the interaction with subjects, which was considered a random factor, thereby minimizing type 1 error and maximizing generalizability [Winer et al., 1991].

RESULTS

Maximum Sound Prolongation

The MyD group performed poorer than the Control group on the Maximum Sound Prolongation task (factor Group: $F(1,28) = 4.20$, $p < 0.05$) as can be seen in Table 2. Both groups showed fairly equal durations for /a/, /z/, and /s/, but shorter durations for /f/ (factor Sound: $F(3,84) = 5.33$, $p < 0.01$). The interaction between Group and Sound was not significant ($F < 1.0$).

Maximum Repetition Rate

The MyD group also performed significantly poorer than the control group on the Maximum Repetition Rate for monosyllabic sequences (factor Group: $F(1,28) = 5.29$, $p < 0.05$), as can be seen in Figure 1. The pattern of relative syllable durations (plosive sequences faster than fricative sequences) was identical for both groups. In order to disentangle the contribution of the duration of the consonant and the vowel, the consonant ratio was calculated: the duration of the consonant (plosive or fricative) was divided by the total duration of the syllable. The MyD subjects produced relatively longer consonants (larger ratios) in the plosive sequences than in the fricative sequences (ratios 0.48 and 0.46, respectively), compared to the control subjects (ratios 0.42 and 0.44); this interaction was significant ($F(1,27) = 4.23$, $p < 0.05$). The latter effect is strongest in the sequences with labial place-of-articulation ("papa.., fafa.."; $p < 0.05$).

Table 2. Mean and standard errors (italics) of Maximum Prolongations of /a, z, f, s/ produced by the 15 MyD and 15 Control subjects

	MyD		Controls	
/a/	21.3	*2.54*	26.5	*2.78*
/z/	19 7**	*2.69*	28.8	*3.54*
/s/	20 8**	*1.97*	32.4	*4.59*
/f/	14.5**	*2.73*	22.6	*5.44*
Overall	**19.1****	***2.54***	**27.6**	***4.20***

Note: Significance level of difference between MyD and Controls·
* $p < 0\,05$
** $p < 0.01$

The MyD subjects produced the multisyllabic sequences, as the monosyllabic sequences, significantly slower than the control subjects (factor Group: $F(1,28) = 5.58$, $p < 0.05$; see Figure 1). More importantly, both the MyD and the control subjects produced the multisyllabic sequences slightly but significantly faster than the monosyllabic ones ($F(1,28) = 6.14$), $p < 0.05$); the *relative* durations of mono- and multi-syllabic sequences is similar across groups.

Pseudoword Imitation

Results of the pseudoword imitation task are presented in Table 3; no omissions were produced by either group. The very slight differences between the MyD and control groups with respect to percentage substitutions, and percentages retention of place- and manner-of-articulation, and voicing were not significant.

Correlations between subject characteristics, MyD-severity indices and speech measures

Correlations between the MyD-subject characteristics age, sex, educational level and age of onset, and the severity ratings MDRS, SI and M (see Table 1), did not prove significant even at the .05 level. As regards the relation between subject characteristics and severity ratings on the one hand, and speech measures on the other, only the correlation between sex and maximum repetition rate of the multisyllabic sequence "pataka.." ($r = 0.609$, $p < 0.05$) was

Table 3. Results of pseudoword imitation task for MyD and control group Presented are· number and percentages of substitutions, and percentages retention of place-of-articulation, manner-of-articulation and voicing; standard errors in italics

	MyD		Control Group	
# substitutions	4.07	*72*	3.27	*.96*
% substitutions	5 02	*.89*	4.03	*1 19*
retention of place %	97.3	*48*	96.9	*98*
retention of manner %	98.3	*57*	98.7	*71*
retention of voicing %	98.6	*.39*	99.0	*44*

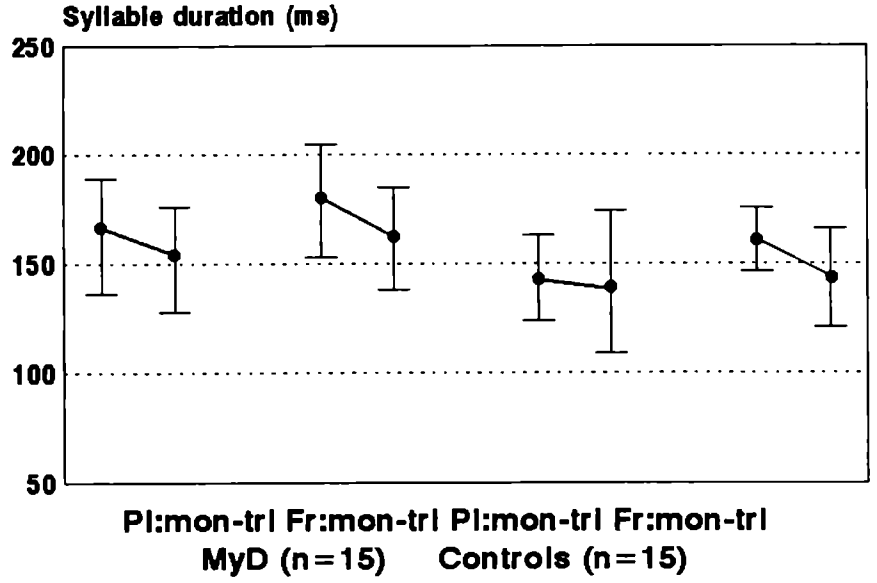

Fig. 1. Mean syllable durations (connected by drawn lines) and standard deviations of the mono- and tri-syllabic plosive and fricative sequences, for the MyD and Control group.

significant; females were slower than males. However, significant correlations were found between the subjective speech assessment by the interviewing speech pathologist and the objective speech measures maximum repetition rate of monosyllabic velar sequences "kakaka.., xaxaxa.." ($r = 0.524$, $p < 0.05$) as well as multisyllabic fricative sequence "fasaxa.." ($r = 0.614$, $p < 0.05$); the five patients with signs of imprecise articulation were slower.

DISCUSSION

Clinical descriptions of mildly affected, early-adult and adult onset MyD patients indicate qualitative speech abnormalities but provide little other information as to the exact nature of the problem. In the present study a quantitative assessment of MyD symptoms was therefore undertaken. The question was whether or not the speech of MyD patients contains apraxic characteristics. In order to answer this question, the difference in Maximum Repetition Rate for multisyllabic and monosyllabic sequences was determined. Previous studies [Maasen et al., 1991; Wit et al., 1993] have shown an overall slowing of both monosyllabic and multisyllabic sequences in dysarthric patients and a slowing of multisyllabic sequences relative to monosyllabic sequences in apraxic patients. The MyD patients in the present study clearly showed a dysarthric profile. That is, the monosyllabic sequences were produced significantly slower by the MyD subjects than by the control subjects, while both of the subject groups produced the multisyllabic

sequences slightly faster than the monosyllabic sequences. This suggests that the MyD speech abnormalities may be limited to motor execution.

Further evidence against the involvement of higher motor programming processes comes from the speech errors produced in the pseudoword imitation task. Only very slight and nonsignificant differences between the MyD patients and control subjects were found. No significant differences were found in the substitution rates or in the retention percentages for place-of-articulation, manner-of-articulation, and voicing information.

A secondary aim of the present study was to establish more firmly the nature of the dysarthria in a group of mildly affected MyD patients. Maximum Sound Prolongation and Maximum Repetition Rate yielded an overall poorer score for the MyD patients when compared to control subjects. Shorter stretches of speech and slowed speech strongly indicate flaccid dysarthria [1]. Moreover, performance on some of the maximum repetition rate sequences correlated significantly with the judgement 'imprecise articulation' of the speech language pathologist.

Two further specifications of the dysarthria are in order.

First, identical profiles were found on the Maximum Sound Prolongation and Maximum Repetition Rate duration measures, which suggests that the muscle weakness observed in the MyD subjects is not restricted to a particular articulatory organ.

Second, the *consonant ratios* for the labial Maximum Repetition Rate sequences were the shortest for the control subjects and among the longest for the MyD subjects. Such high consonant ratios reflect problems with rapid alternating movement of the lips (and jaw). Furthermore, in contrast to the control subjects, the MyD subjects produced systematically higher consonant ratios in the plosive sequences than in the fricative sequences. In plosive sequences a complete occlusion of the vocal tract is made, which requires more muscle activity than in fricative sequences, where incomplete occlusion suffices [Harris et al., 1985]. The relatively high consonant ratios indicate overshoot rather than undershoot in the production of plosives by the MyD subjects. Taken together, the results suggest the effects of myotonia: the inability to relax in particular the lips, where the increase of the consonant ratio is most prominently present. The absence of significant correlations between motoric severity ratings, which reflect weakness in particular, and speech measures further supports this interpretation.

To summarize: A procedure to quantitatively assess the integrity of speech motor execution and speech motor programming was applied to a group of mildly affected, early-adult and adult onset MyD patients. From the absence of apraxic signs, it can be concluded that there is no involvement of speech motor *programming*. The observed speech motor *execution* signs point to flaccid dysarthria. Relative differences between MyD and control subjects can tentatively be interpreted as the result of myotonia, particularly in the perioral musculature.

With the quantitative assessment procedure used in this study, one of the signs of MyD in an early phase can be detected. Moreover, an objective instrument is available to evaluate the results of therapy, that might be developed in the near future.

CHAPTER 5.1

COGNITIVE FUNCTION IN EARLY ADULT AND ADULT ONSET MYOTONIC DYSTROPHY WITH MILD SYMPTOMS: NEUROPSYCHOLOGICAL AND MOTOR EVIDENCE

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INTRODUCTION

Myotonic dystrophy (MyD) is an autosomal dominant multisystem disease with a variable clinical expression. The primary genetic defect is an increased number of cytosine-thymidine-guanine (CTG) trinucleotide repeats in the 3' untranslated sequence of a gene, located at the q13.3 band of chromosome 19 (Aslanidis et al., 1992; Buxton et al., 1992; Harley et al., 1992). Expansion of the CTG repeat correlates with early onset and severity of MyD (Buxton et al., 1992; Brook et al., 1992). The principal symptoms are myotonia, slowly progressive weakness and atrophy (Harper, 1989), but, since MyD is a multisystem disease and the genetic deficit is present in every cell, symptoms and signs arise in several tissues and organs (Moxley, 1992). Cognitive impairment is common in MyD and is often the most disabling component of the disease. Most studies in MyD showed mild to severe intellectual deficits (Woodward et al., 1982; Bird et al.,1983; Portwood et al., 1986; Perini et al., 1989; Walker et al.,1984; Malloy et al., 1990; Censori et al., 1990; Ragazzoni et al., 1991; Chang et al., 1993), but some did not (Brumback, 1987; Franzese et al., 1991). The diversity of these findings depends largely on the composition of the group of patients under study (Stuss et al., 1987; Huber et al., 1989), but also on the way in which cognitive functioning was assessed. Accordingly, if one intends to investigate cognitive functioning in MyD, it is necessary to study homogeneous groups. Furthermore, some studies only assess global intelligence, some studies also measure more subtle cognitive functions of which impairment may occur in absence of diffuse intellectual deterioration. Despite a normal IQ profile, Chang et al., (1993) did not find any completely normal SPECT in a homogeneous subgroup of MyD patients with parental inheritance and with early adult and adult onset. Thus, it is not at all excluded, that these patients might have shown discrete cognitive dysfunctions in a more detailed neuropsychological assessment. As far as we know, the study of Franzese et al. (1991) is the only one which investigated a homogeneous group of patients, but with a very restricted test battery, and there are no studies, which investigated cognitive functioning in a homogeneous group of MyD patients as well as with a broad spectrum of neuropsychological tests.

The aim of the present study was to investigate whether normal intelligent MyD patients with early adult and adult onset show subtle cognitive dysfunction. We compared a homogeneous group of mildly disabled patients without mental retardation and with early adult and adult onset MyD and a group of matched control subjects (CS) on a range of neuropsychological tests and motor tasks of increasing complexity, which required correspondingly more cognitive control. With respect to the motor tasks: if MyD impairs cognitive control of motor performance, patients suffering from MyD will show a greater drop in performance from simple to complex motor tasks, than CS.

MATERIALS AND METHODS

Subjects

The patients included in this study are members of kindreds with classical myotonic dystrophy according to the diagnostic criteria of Griggs and Wood (1989). All patients had an early adult and adult onset, that is an onset between the ages of eleven and forty-five years in terms of the criteria of Koch et al. (1991). Patients with non-MyD symptoms, with sleep apnoea (Broughton et al., 1990), or using drugs, that might interfere with test performance, were also excluded. Patients with an IQ ≤ 80, impaired vision or hearing and a Karnofsky disability-score < 70 (Karnofsky, 1949) were also excluded from this study. We used two rating scales to assess muscular disability: the Muscular Disability Rating Scale (MDRS) (Mathieu et al.,1992) and the scale of the Medical Research Council (MRC) (1982). Eventually, twenty-four patients participated in this study. All gave informed consent. We added 2 patients with a diagnosis of MyD on the basis of DNA linkage studies and positive pedigree structure (Brunner et al., 1989). Thus, the total group consisted of 26 patients. Seven patients had maternal, and fourteen had paternal inheritance. In five patients inheritance was unknown. All patients scored below the cut-off score of the Zung depression scale (Zung, 1965). A sample of 24 healthy control subjects (CS), matched for age, IQ and educational level, was obtained from relatives and hospital employees. Table 1 summarizes some demographic and clinical data.

Table 1. *Demographic and clinical characteristics of patients suffering from myotonic dystrophy (MyD) and control subjects*

	MyD	CS
Number	26	24
Ratio male/female	13/13	9/15
Age	35.6 (10.3)	38.3 (10.3)
Educational level (yrs)	10.2 (3.8)	9.5 (3.4)
WAIS-IQ	107.6 (18.3)	110 9 (15.1)
Age at onset	24 8 (8.9)	
Duration (months)	121.1 (102.5)	
Maternal inheritance	7 (26%)	
Paternal inheritance	14 (54%)	
Inheritance unknown	5 (19%)	
Karnofsky score	83.8 (9.4)	
MRC sum score	51 (5.2)	
MDRS	2 9 (0.6)	
Dysarthria	18 (70%)	

MRC Medical Research Council scale
MDRS: Muscular Disability Rating Scale

Methods

We selected neuropsychological tests which assess a broad spectrum of cognitive functions, such as memory, maintaining set, visuospatial scanning, fluency and executive function, besides global intelligence. Impaired executive functions are extensively documented in frontal lobe dysfunction, but also in diseases with subcortical degeneration (Albert, 1978), such as Parkinson's disease (Cools et al., 1984; Taylor et al., 1986; Cummings, 1988), Huntington's disease (Caine and Fisher, 1985; Starkstein et al., 1988; Bamford et al., 1989), supranuclear palsy (Milberg and Albert, 1989) and multiple system atrophy (Robbins et al., 1992).

To assess intelligence we made a valid and reliable selection of four subtests from the revised Wechsler Adult Intelligence Scale (WAIS-R): vocabulary and similarities, measuring verbal intelligence, and picture completion and block design, measuring visuoperceptual intelligence (Cyr and Brooker, 1984). Memory was assessed by means of the California Verbal Learning Test (Delis et al., 1987). We selected the CVLT, because this test not only provides a measure of the amount of information that a subject is able to remember, but also a multi-factor framework for quantifying his learning strategies. The CVLT is composed of two shopping lists, each containing 16 common items bought in stores. The 16 items on each list are presented in random order. Each item belongs to one of four semantic categories embedded in the test (i.e. clothing, tools, fruit and spices). The first list was read aloud by the experimenter for a total of five trials. Test protocols were scored using the IBM-PC California Verbal Learning Test scoring program (Fridlund and Delis, 1987). Score was the total number of words recalled over the five trials. The semantic and serial cluster ratio reflected the semantic, respectively serial clustering tendency, both being learning strategies. It was obtained by dividing the observed cluster score (i.e. the total number of semantically clustered words) by the cluster score expected by chance. A decrease of semantic clustering (Taylor et al., 1990; Buytenhuijs et al., 1994) and an increase of serial clustering (Buytenhuijs et al., 1994) are established in Parkinson's disease, and might therefore be linked with subcortical dysfunction. We included a variety of tests measuring executive functions (Lezak, 1983). The Stroop Colour Word Test involves the ability to inhibit a well-rehearsed response in favour of a counter-intuitive one (Jensen and Rohwer, 1966). The test consists of three cards. The subject had to read words, each designating one out of four colours (red, blue, yellow and green), printed in black ink on card A, then name the colour of coloured bars, printed on card B, and finally, name the colour of the ink, in which words designating a different colour were printed (card C). For example, when the word 'green' is printed in red ink, the correct response is 'red'. Score was the time in seconds needed by a subject for each card. The score of interference was calculated by subtracting the score of card B from that of card C, thus extracting speed of performance. The Trail Making Test (TMT) consists of the sections A and B (Reitan, 1958). Initially, in section A the numbers 1–25, randomly distributed on a sheet of paper, had to be connected

in order with a pencil line as quickly as possible. In section B, the numbers 1–13 and the letters A–L (again randomly distributed) had to be connected in order using an alternating number-letter sequence. The score was the time difference between section A and B (B–A). This removed the effect of motor speed from performance. The Verbal Fluency tests (VFT) required the subjects to enumerate as many animals as possible during one minute. The score was the number of items generated. The Wisconsin Card Sorting Test (Berg, 1948) is a categorization test. In this test the subject began to sort on the basis of trial and error according to a criterion that was only known to the experimenter. A false response was corrected by the experimenter. After a fixed number of correct responses the experimenter changed the criterion twice without informing the subject. In order to exclude biasing differences in speed of information processing there were no time constraints. Performance was reflected in the number of categories the subject discovered (Bowen, 1976), and the total number of trials he needed (Van Spaendonck et al., 1993).

We presented a range of motor tasks to be performed by each hand separately (Perret et al. 1970; Cools et al., 1984). For these tests, keyboards were constructed with four push-buttons. Measurement of pushes was computerized. Before starting the motor tasks the patients were asked to clench their hands as often as they needed to get rid of stiffness. Motor ability was assessed in a number of tasks of increasing complexity. The first was classical diadochokinesis of each hand separately. The other tasks were finger tapping tasks of increasing complexity. In the first three tasks, the subjects had to press one push-button with the index finger as fast as possible for a period of 5 s. Then they had to press all push-buttons with the index finger. Next, they had to place the four fingers on the buttons and to push the buttons in a random sequence for 10 s. In the following series complexity with respect to response planning and motor programming increased (Schmidt, 1982 and 1988; Mulder, 1991). The subjects had to press the push-buttons in a fixed sequence of increasing complexity, firstly, index finger – middle finger - ring finger – little finger; next, index finger – ring finger – middle finger – little finger; and finally, they had to shift from the first and simple sequence to the second and more complex one. The latter task enables us to differentiate between response planning and motor programming: if performance of MyD patients is significantly poorer than that of CS in the shifting condition, but not in the two prior conditions, then it seems plausible there is an impairment in the non-output specific planning, i.e. on the level of response planning, rather than in the output specific motor programming. The following scores were computed: the total number of pushes in each task; the total number of correct successive pushes in the shifting task (a push was counted as correct when it was preceded or followed by the correct push as defined in the sequence).

RESULTS

Table 2 summarizes means, standard deviations and t tests of the neuropsychological test scores. The groups of patients and CS were matched for intelligence.

Table 2. Means and standard deviations of neuropsychological test scores level of significance is associated with t values

	MyD (n = 26)		CS (n = 24)		significance of t
	Mean	sd	Mean	sd	p
CVLT					
first shopping list					
immediate recall	57 64	10 52	60 06	8 68	ns
semantic ratio	1 95	0 74	2 18	0 72	ns
second shopping list					
immediate recall	8 14	2 60	7 61	2 30	ns
first shopping list					
short term	11 90	3 10	12 98	2 27	ns
free recall					
short term	13 27	2 91	13 94	1 77	ns
cued recall					
long term	13 18	2 86	13 78	2 07	ns
free recall					
long term	13 45	2 63	14 06	1 77	ns
cued recall					
Stroop A	49 48	10 03	42 88	8 13	< 05
Stroop B	64 64	11 56	54 79	10 08	< 005
Stroop C	115 48	21 48	90 58	19 70	< 0001
Stroop C-B	50 80	13 40	35 79	12 63	< 0005
TMT A	38 92	17 18	32 86	14 91	ns
TMT B	93 50	37 60	77 43	35 90	ns
TMT B-A	54 00	22 61	44 57	26 08	ns
Verbal fluency	19 54	4 63	22 13	5 47	ns
WCST sum categories	3 73	0 45	3 79	5 47	ns
WCST sum trials	22 00	13 93	21 21	13 61	ns

Globally, the Myd patients did perform as well as the CS on all tests. With respect to the CVLT we also tested whether the learning performance of the MyD and that of CS differed over the five trials. A MANOVA test revealed that there was no group x trial interaction: $F = 1.33$ (ns). There were no significant differences between the groups with respect to the semantic and serial cluster ratios. Thus, we did not find any indication of cognitive impairment, with the exception of the Stroop Colour Word Test. Even after correction for speed of performance by subtracting time of performance of the

simple Card B from that of the complex card C, the scores of the MyD patients remained significantly higher than those of CS

Table 3 summarizes means, standard deviations and t tests of the motor scores

Table 3. Means and standard deviations of motor scores level of significance is associated with t values

	MyD (n = 26)		CS (n = 24)		significance of t
	Mean	sd	Mean	sd	p
diadochokinesis DH	11 8	4 6	16 7	2 7	< 0005
diadochokinesis NDH	10 9	4 8	16 0	3 1	< 0005
Tapping tasks					
index one button DH	21 9	6 3	25 5	4 0	< 05
index one button NDH	19 8	5 6	23 9	3 4	< 01
index four buttons DH	9 1	3 5	12 6	6 0	< 05
index four buttons ND	8 7	3 8	12 4	5 0	< 01
free sequence DH	24 6	9 1	37 5	20 1	< 05
free sequence NDH	23 2	7 9	29 7	10 2	< 05
1–2–3–4 DH	21 9	7 9	29 3	9 7	< 01
1–2–3–4 NDH	21 3	8 0	27 1	8 6	< 05
1–3–2–4 DH	17 5	6 7	19 4	7 9	ns
1–3–2–4 NDH	17 8	8 4	18 5	8 2	ns
Shifting tasks					
1–2–3–4 DH total	20 6	7 7	27 0	8 2	< 05
1–2–3–4 NDH total	21 5	7 3	26 1	8 3	ns
1–2–3–4 DH correct	18 8	8 6	20 7	9 2	ns
1–2–3–4 NDH correct	19 3	6 3	19 8	9 1	ns
1–3–2–4 DH total	17 6	7 9	19 5	7 6	ns
1–3–2–4 NDH total	16 6	7 9	18 5	9 0	ns
1–3–2–4 DH correct	14 6	7 1	15 3	6 5	ns
1–3–2–4 NDH correct	12 8	7 9	13 0	9 0	ns

DH dominant hand
NDH non-dominant hand
total total number of pushes
correct number of correct pushes

MyD patients showed a significantly poorer performance on simple tasks. However, the difference between the groups decreased on more complex tasks, that required increasingly cognitive control. In the most complex task, i.e. the shifting task, the difference between MyD patients and CS has disappeared.

Since we were interested in the relationship between the measures, which differentiated between the groups, we calculated the correlations (Pearson's r) between the motor scores and the scores of the Stroop Colour Word Test in both groups.

Table 4. Correlations between scores of motor tests and Stroop performance· level of significance is associated with Pearson's r

	MyD (n = 26)			CS (n = 24)		
Stroop card	A	B	C	A	B	C
diadochokinesis DH	− 21	03	−.02	.01	.05	−.15
diadochokinesis NDH	− 25	22	.25	−.08	.10	.08
Tapping tasks:						
index one button DH	−.15	−.28	−.45*	−.28	−.25	− 02
index one button NDH	−.16	−.26	−.41	−.32	−.30	−.07
index four buttons DH	.03	−.24	−.42	−.22	−.29	−.31
index four buttons NDH	−.01	− 22	−.38	−.23	−.21	−.21
free sequence DH	.01	−.27	−.33	.29	.10	−.13
free sequence NDH	−.04	−.33	−.42	.10	−.09	−.12
1–2–3–4 DH	.11	−.28	− 34	− 41	−.35	−.36
1–2–3–4 NDH	.01	−.28	−.38	−.36	−.27	−.26
1–3–2–4 DH	−.06	−.43*	−.50*	−.29	−.25	−.22
1–3–2–4 NDH	−.10	−.47*	−.57**	−.28	− 26	−.26
Shifting tasks:						
1–2–3–4 DH total	−.01	−.42	−.49*	−.36	−.27	−.28
1–2–3–4 NDH total	−.09	−.47*	−.49*	−.33	−.25	−.21
1–2–3–4 DH correct	− 05	−.42	−.51*	−.22	−.18	−.02
1–2–3–4 NDH correct	.09	−.35	−.44*	−.14	−.12	.02
1–3–2–4 DH total	− 11	−.47*	−.57**	−.32	−.33	−.34
1–3–2–4 NDH total	−.09	−.45*	−.58**	−.35	−.35	−.36
1–3–2–4 DH correct	−.27	−.54**	−.58**	−.21	−.24	−.12
1–3–2–4 NDH correct	−.16	−.48*	−.63#	−.52*	−.49*	−.45

DH: dominant hand
NDH: non-dominant hand
total: total number of pushes
correct: number of correct pushes
* $p < .05$ ** $p < .01$ # $p < .005$

There was no relationship between the scores of the motor tasks and the simple card A in either group. Only in the MyD patients some scores of complex motor tasks correlated with card B, and all scores with card C.

DISCUSSION

The purpose of the present study was to investigate whether patients with early adult and adult onset MyD show subtle cognitive dysfunction despite a normal intelligence. For this reason, we excluded all MyD patients with mental retardation. This enabled us to examine whether a homogeneous group of MyD patients with only mild disability, as reflected by the Karnofsky scores and the muscular rating scales, shows a more discrete pattern of cognitive impairment. We compared these patients with a group of CS, matched for age, intelligence and educational level, on a range of neuropsychological tests,

measuring a broad spectrum of functions: memory (CVLT), attention (Stroop), visuospatial scanning (TMT), verbal fluency and cognitive shifting (WCST). As already indicated in the introduction, we selected these tests, because performance of these tests is impaired not only in patients with cortical dysfunction, but also in patients with subcortical dysfunction.

The MyD patients and CS did not differ in performance on these tests, with the exception of the Stroop Colour Word Test. Our results are not in accordance with studies, which did not exclude patients with infantile and juvenile MyD (Woodward et al., 1982; Bird et al.,1983; Portwood et al., 1986; Huber et al., 1989; Perini et al., 1989; Walker et al.,1984; Malloy et al., 1990; Censori et al, 1990; Ragazzoni et al, 1991), but are fully in agreement with the study of Franzese et al. (1991), as far as we know the only study that involved only early adult and adult onset patients. In the latter study, fully normal IQ-scores are reported. With regard to the Stroop Colour Word Test, MyD patients gained significantly poorer scores on all cards. Nevertheless, they scored better than the patients in the study of Broughton (1990). Our patients also scored better than the MyD patients and CS in the study of Stuss et al. (1987), but the CS in that study, who were matched with MyD patients for intelligence, showed a dull normal mean IQ (WAIS-R) = 87.1. However, the subgroup of late onset MyD patients in that study produced only slightly poorer scores than our patients. Apparently, the distinct findings are due to the composition of the groups under study. The results of the present study emphasize the necessity to have homogeneous groups. Some authors (Brumback, 1987; Malloy et al., 1990) found visuospatial and constructional disabilities, suggesting greater right hemisphere dysfunction in MyD, but this hypothesis is not supported by the finding in the same studies and in ours, that there are no significant differences in tapping performance between the right and left hand. In a heterogeneous group of 22 MyD patients, Chang et al. (1993) found significant correlations between right hemisphere perfusion and visuospatial skills (Hooper Test, Visual Reproduction), but also between left temporo-parietal perfusion and Performance-IQ, a measure which also reflects visuospatial skills. Thus, an exclusive relationship between right hemisphere dysfunction and visuospatial or constructional impairments in MyD is uncertain. An overall reduction of speed itself might also account for poorer performance of MyD patients in visuospatial tasks. Therefore, we recommend correcting neuropsychological task performance of MyD patients for both speed and intelligence: the visuospatial and constructional disabilities, that are established in the studies mentioned above, might not stand such a correction. Many studies (Bird et al., 1983; Portwood et al., 1986; Huber et al., 1989; Censori et al., 1990; Koch et al., 1992; Chang et al., 1993) revealed more cognitive impairment in patients with maternal inheritance than in patients with paternal inheritance. In the present study, patients with maternal inheritance (n = 7) showed a poorer performance overall than the patients with paternal inheritance (n = 14), but the difference was only significant in the

immediate recall of the second shopping list of the CVLT. The lack of significance might be due to sample sizes.

The selective poor performance of MyD patients with respect to the Stroop Colour Word Test is not easy to interpret. This test is based on a conflicting response paradigm (Dyer, 1973): the first and most automatic response is reading words (Card A), the second response is simple, but less automated: naming colours (card B). Finally, in Card C the subject is required to suppress the automatic response (reading words) in favour of the less automated response (naming colours). Since our MyD patients produced poorer scores on all cards, a retardation of information processing is plausible. Our MyD patients were also slower than CS in the TMT, but this difference did not reach significance. Since the Stroop performance of MyD patients worsened, as the complexity of the task increased, they appear to be sensitive to response interference. However, our data also allow a different interpretation. In the majority of our MyD patients (see Table 1), dysarthria was already clinically established during normal speaking. Because of this – MyD coupled – dysarthria (see also Harper, 1989), speaking aloud and as fast as possible, is a more effort demanding task for MyD patients than for CS, which is reflected in the significant lower scores on cards A and B. Therefore, it seems plausible, that in the case of MyD patients, simultaneously speaking fast and reading the difficult card C required a dual task performance. Previous research has shown that performance of the Stroop Colour Word Test significantly affects the performance of a concurrent motor task, viz. control of balance after lower limb amputation in normal subjects (Geurts et al., 1991). Further research will be needed, involving a test of the Stroop paradigm, but without an appeal to fluently speaking. Anyhow, in our view the lower performance of the Stroop Colour Word Test does not necessarily imply a central cognitive deficit, but may also be due to a peripheral defect. The significant difference in Stroop performance between the two groups clearly does not interfere with any other cognitive function under study, simply because there are no other differences. To summarize, these findings indicate that MyD patients of normal intelligence with early adult and adult onset show any or no cognitive impairment. We also presented a number of motor tasks of increasing complexity, which required correspondingly more cognitive control. The scores of all motor tasks showed very low correlations with any disease variable or rating scale. This last finding is not surprising, since both the MRC-scale and MDRS assess muscular weakness, a disease characteristic, which played a minor part in our motor tasks. The MyD patients produced significantly poorer scores than the CS on simple tasks. The difference between the groups reached the highest significance in diadochokinesis, being the most automatic one in our series. The difference between the groups disappeared in tasks in which performance depends less on speed of motor execution, but more on response planning and motor programming, i.e. cognitive control. It was only in the simple sequence (index – middle finger – ring finger – little finger), that MyD patients scored significantly worse than CS. In the complex sequence (index

– ring finger – middle finger – little finger) the scores of MyD patients were no longer significantly different from those of CS. A plausible explanation for this finding is that the simple sequence approximates an automatic one. Since we did not find any significant correlation between the Stroop scores and simple motor performance, the significant group differences in simple motor tasks cannot be attributed to the significant differences in Stroop performance between the groups. Complex motor sequence performance is known to deteriorate in diseases with central programming deficits, such as Parkinson's disease (Cools et al. 1984; Benecke et al. 1987; Harrington and Haaland, 1991). Our results indicate that the cognitive control of motor performance is not impaired in MyD. Our findings lead us to conclude that MyD patients with mild symptoms, normal intelligence, and early adult and adult onset do not show cognitive dysfunction. In turn, this indicates that in this group of patients there is no evidence of brain dysfunction, such in spite of an ubiquitous genetic deficit.

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CHAPTER 6

GENERAL DISCUSSION

and

EPILOGUE

GENERAL DISCUSSION

In this thesis a number of quantitative functional assessments are presented that refer to different aspects of organ involvement of MyD. Seventy-five adult-onset patients were included in the current study. In the following paragraphs, the results of neuro-ophthalmologic, neuro-otologic, bulbar and neuro-psychologic symptoms and signs will be summarized. Subsequently, the main findings will be discussed in relation to the literature on systemic involvement in MyD and on the current views on genetics.

Neuro-ophthalmology

With regards to the visual system, the functions of the extra-ocular muscles (chapter 2.1-2.3), retina (chapter 2.4) and optical nerves have been studied (chapters 2.1, 2.3 and 2.4) as well as visuospatial functions (see chapter 5, neuro-psychology).

Eye movements. In 31 patients, without pronounced mental involvement, the pattern of eye movements was studied. In total, 26 patients had their onset in adult life with only one patient complaining of diplopia. The main eye-movement disorder in the classical form of MyD is an isolated sub-clinical decrease of maximum velocity (Vmax.) of the horizontal visually guided saccades. The slowing of the saccades is a rather early and progressive sign, that correlates weakly with the severity of the neuromuscular deficit (Mathieu-score). The pathophysiological mechanism is based mainly on myopathy of the extra-ocular muscles. The group of Bollen et al. (1992) disagreed and suggested, in accordance with temporal MRI findings, a central abnormality as the cause of eye-movement disturbances due to the more pronounced smooth pursuit gain decrease.

Perhaps, the different patient selection by Bollen et al., i.e. congenital cases with hypersomnolence, may be a better explanation than heterogenicity. However, we would add that secondary, 'central' adaptation mechanisms, may also play a role in oculomotor function as demonstrated in our study of neuro-otological signs.

Retinopathy. In chapter 2.4, the functional abnormalities of the retina were described for a group of 12 MyD patients among whom, 8 were of mild severity and 4 were asymptomatic gene carriers. In total, 7 out of 8 were classified as adult onset. In contrast to all previous studies, we found the cones, the foveal photoreceptors and the RPE (retinal pigment epithelium) to be more commonly affected than the rods in this minimally affected group. Thus, retinopathy is an 'early phenomenon' with an unknown but progressive course (Yoshihiro et al., 1993). We assume that a diffuse degeneration of the rods and other retinal layers occurs only in later phases of the disease. None of the retinal findings showed a correlation with the neuromuscular deficit (scores converted to the Mathieu-score).

Optical nerves. Chapter 2.1-2.3 and 2.4 deal with the optical nerve functions in MyD. The subclinical changes were studied by pattern VEP (pVEP) in 44 patients, of whom 40 were classified as adult onset. The pattern for an adult onset group can be characterized by a bilaterally prolonged P100 latency and diminished amplitude. The former results correspond with previous studies (Gott et al., 1983, Kerty and Ganes, 1989). The pVEP changes are probably a rather 'early' phenomenon (Gott et al., 1983) with a progressive course, that correlated with the latency of the visually guided saccades and slightly with the neuromuscular deficit (Mathieu-score).
We found in a group (N=12) of mainly adult onset MyD patients, a trend between P100 latency and foveal two-way-densitometry findings (chapter 2.4). Therefore, we assume a bilateral optical nerve degeneration, secondary to the above described retinal processes. This is in accordance with the opinion of Junge (1966), whilst Kerty and Ganes (1989) proclaimed an altered processing within the visual cortex as an explanation for the VEP changes. This is unlikely for the group studied, due to the intact colour vision and normal MRI findings of the occipital cortex (Damian et al., 1992).

Neuro-otology

In chapter 3 the results of oculomotor, auditory and vestibular tests have been described for an adult onset group of 13 MyD patients. Twelve of them were classified as adult onset. None of the patients complained about vertigo. Our observations showed sensorineural high tone loss, frequent abnormal VOR (vestibulo-ocular reflex) as well as central abnormalities in the acoustic pathways (prolongation of BAEP I-V interwave delay). Our results are in agreement with previous authors (Kuhn and Ey, 1966; Wright et al., 1988).
The hearing loss in the 'classical group' has its onset in adult life and the course is definitely progressive and slightly related to neuromuscular deficit (scores converted to Mathieu-score).

Bulbar dysfunction

Swallowing. In chapter 4.1 we studied the function of swallowing in 26 adult onset MyD patients. The duration of swallowing was significantly prolonged in the MyD patients. Even in the early phase of the disease, difficulties with swallowing may occur which are unrelated to the complaints of dysphagia (Horowitz, 1987a,b), while the course appears to be progressive (this study). The swallowing disorder in this study correlated slightly with the severity of limb muscle weakness (Mathieu-score). Our results correspond with another single published quantitative study using a videofluoroscopic technique that reports a prolonged pharyngeal transit time (Johnson et al., 1993). In the early phase, myotonia is held responsible for dysphagia (Bosma and Brodie, 1968), while in the later phase the myopathy of striated muscles in the upper

pharynx are supposed to predominate in the swallowing disorder (Eckhart et al., 1986).

Speech. In chapter 4.2 we investigated the function of speech in 15 mildly affected adult onset MyD patients using a quantitative computerized speech analysis. A flaccid dysarthria with absence of dyspraxia is a noticeable feature. The speech disorder is undoubtedly an 'early' onset phenomenon, with a progressive course (Thomasen, 1948; Harper, 1989), unrelated, in this study, to the neuromuscular deficit (Mathieu-score; chapter 4.2).

The speech in the adult onset MyD group can be characterized by a poor sound prolongation and a reduced repetition rate which together, lead to shorter stretches of speech and slowed speech. Apart from the predominant flaccid dysarthria, we also presume that myotonic phenomena, particularly in the (peri)oral muscles, influenced the speech disorder in our group.

Neuro-psychology

In chapter 5, we investigated the cognitive and motor functions in a group of 26 normal intelligent adult and early adult onset MyD patients with mild symptoms. In the investigated group, the only abnormal findings were present in a test for selective attention (Stroop Colour Word Test, SCWT) and for hand motor execution. Although SCWT scores correlated with motoric test scores, no significant correlation was found between test scores and clinical scores of hypersomnolence, inheritance pattern or neuromuscular deficit (Mathieu-score). However, a correlation trend was found between SCWT results and maternal inheritance.

On its own, a SCWT alteration is an aspecific finding which might be related to defective selective attention or a more general information processing capacity. It is argued that poor SCWT performance is not strictly due to cerebral involvement. Rather, it may be the result of the higher demands which this task puts on the MyD subjects as a result of poorer speech motor function. The abnormal SCWT finding does not contradict the studies of Stuss (1987) and Broughton (1990).

However, the visuo-spatial and visuo-constructive tasks were within the normal range in our study. In other neuro-psychological studies this was the most common finding with regards to MyD (Censori et al., 1990). The relationship between visuo-spatial and visuo-constructive dysfunction and the bilateral fronto-parieto-temporal localization of neuroradiological and morphological findings is curious or perhaps spurious. The prevailing view of the neuro-psychological studies is that they reflect an unknown and subtle developmental abnormality of the cerebrum, chiefly involving the non-dominant hemisphere functions. This occurs more often in MyD patients with an earlier onset than in patients with adult onset. Alternatively, a more likely interpretation of the cognitive impairment pattern might be due to heterogenous group composition in previous studies. Another option is to consider the disturbances of the visuo-spatial and constructional functions as a non-spe-

cific phenomenon due to bilateral cerebral involvement (Lezak, 1983), e.g. caused by widespread neurofibrillary changes (Yoshimura, 1990). Moreover, Franzese (1991) found in his adult onset group, that *only* in the group with low intelligence (7%), were there alterations of the visuospatial functions.

In conclusion, our results are not in agreement with other neuro-psychological studies. So far, for the cognitive dysfunction in the adult onset group there is no unanimity and the results are insufficiently reproducible. Presumably, most groups studied have been inhomogeneous and are consequently incomparable with one another. This issue might be solved by studying cognitive function, using a few carefully selected tests in larger numbers of adult onset patients with a short and a longer duration of the disease.

What are the implications of the current views in genetics on clinical signs and symptoms of MyD?

The impact of genetics in MyD will be subdivided into practical consequences and the acquired insight with regards to MyD basic mechanisms. Furthermore, we will discuss the clinical variability of the disease.

First, the *practical consequences*. Nowadays, DNA analysis is the golden standard for diagnosis. No diagnostic gain is to be expected from clinical studies as the accuracy of DNA analysis is almost 100% now, (Wieringa, 1994 a.o.). After performing a neurological investigation, an EMG and a slitlamp examination, the minority, (approximately 8%) of MyD patients remain undetected (Brunner et al., 1991). Therefore, only EMG and slitlamp examination remain useful diagnostic tools, whilst in fact tonometry should be listed as well, due to its high specificity (Ashizawa et al., 1992). However, sporadic and 'aspecific' (white dots) lens inclusions are not often reasons for diagnostic confusion and unnecessary genetic studies (Brunner et al., 1991; Ashizawa et al., 1992).

Slitlamp examination should be employed carefully and should be carried out by an experienced ophthalmologist (Ashizawa et al., 1992).

DNA analysis has to be performed at least in 1 person in an affected family. Certainly, the diagnosis of MyD in asymptomatic family members or in cases where there is doubt, has to be confirmed or excluded by DNA techniques. Based on knowledge derived from genetic studies, the clinical subdivision in the age of onset groups makes sense due to the broad correlation with (CTG)n repeat length. Nowadays, the consequences of the somatic variability in (CTG)n amplification for various tissues within the same patient, remain obscure. Therefore, for predicting the prognosis and future severity of the disease, the possibilities of DNA methods are still limited. One exception is that all patients with a mild form (CTG repeat excess 100-120) usually have cataracts as the sole symptom.

Secondly, the concept of a dynamic (CTG)n repeat, highlighted some longstanding and *incompletely understood features* of MyD. The principle of

anticipation, (an earlier occurrence in later generations), can be explained in this way. In adult onset patients, the (CTG)n repeat length in sperm does not allow further prolongation than 1000 (Lavedan et al., 1993; Mulley et al., 1993; Brunner thesis, 1993). The exclusive maternal inheritance of congenital dystrophy cases is probably due to negative selection during the spermatogenesis (Brunner, thesis, 1993).

Recent investigations also raise new questions with regards to the variability of systemic involvement of patients belonging to the same disease type and finding accumulating evidence for a variable (CTG)n excess in separate tissues within a MyD patient.

Concerning the enormous clinical variability, some incomplete correlations with the genetic abnormality can be outlined: an earlier age of onset and a greater severity, broadly correlates with a (CTG)n repeat excess (Harley et al., 1993). Therefore, a clinical subdivision in the *age of onset* groups has been used in the analysis of genotype/phenotype relationships. However, the overlap in (CTG)n excess shows that other influences should be taken into account. For example, the extent of myotonin-proteinkinase (MT-PK) mRNA also showed a correlation with the *severity* of the limb muscle weakness (Pizzuti et al., 1993).

The majority of the genotype-phenotype correlative studies, refer to the severity of limb muscle weakness. However, the correlation between DNA expansions and clinical *severity* is also valid when *single symptoms* are analyzed in patients with MyD. Novelli et al. (1993) measured the (CTG)n expansion in 107 MyD patients using an arbitrary clinical scale for scoring different parameters such as muscle hypotonia, myotonia, cardiac manifestations, ocular findings and mental status. As was to be expected, the strongest correlation was found between (CTG)n repeat and muscle involvement (myotonia< atrophy< severe weakness). The presence of overt mental retardation and some ocular findings also slightly correlated with the CTG repeat length.

Because half of the genome is needed to specify the manifold brain function, it is not surprising that mental impairment is a consistent component of expansion disorders (Wieringa, 1994).

To date, we must conclude that genotype-phenotype correlation is complex and determined by many factors (Brunner, 1993a,b; Cobo, 1993; Wieringa, 1994). As described in this thesis, the dynamic mutation responsible for MyD must have different effects on several tissues. One of the attractive alternatives is a different genetic abnormality per organ system, also termed *somatic mosaisims* or - heterogeneity. This assumption receives increasing support from recent studies.

A different (CTG)n repeat length is found in sperm and leucocytes (Janssen et al., in press), in muscle cells and leucocytes (Anvret et al., 1993; Ashizawa et al., 1993; Thornton et al., 1994) and in several tissues of an adult onset MyD patient (Janssen et al., 1994). Consequently, a genetic heterogeneity may also be suggested in the several organ systems in the adult onset group with mild

severity, as investigated in this thesis.

Nevertheless, as long as knowledge with regards to the cellular effects of the (CTG)n expansion remains limited, the question of variable expressivity, (type of symptoms, severity and course), will remain unanswered.

Main conclusions from this thesis

1. An isolated and progressive slowing of maximum velocity (Vmax.) of the visually guided saccades is the predominant eye movement disorder. Myopathy of the extra-ocular muscles is most likely to be the underlying pathophysiological mechanism.
2. In the 'early' phase of adult onset MyD, a dysfunction of cones and photoreceptors occurs first, while subsequently a diffuse degeneration arises.
3. It is suggested that the neuropathy of the optical nerves is secondary to the retinal processes.
4. Both peripheral and central neuro-otological abnormalities occur in MyD. The sensorineural hearing loss and other neuro-otological deficits in MyD are progressive.
5. A disturbance of swallowing in the adult onset form of MyD is progressive. The dysphagia is only faintly related to the severity of limb muscle weakness, indicating a different pattern of involvement.
6. The dysarthric speech in mild phases of adult onset MyD can be characterized as 'flaccid dysarthria', with normal speech programming. Furthermore, myotonia in the perioral muscles has an influence on the speech motor execution.
7. The noticeable feature of cognitive dysfunction in adult onset MyD with mild severity, is supposed to be a prolonged duration on Stroop Colour Word Test with normal visuospatial- and constructive functions.
8. In the adult onset group with mild severity, bulbar and distal limb muscles and the eye are more frequently involved than the neuro-otological system and cerebrum.
9. Variability of clinical features is a hallmark of MyD. A marked reduction in clinical variability can be generated by including age of onset, degree of severity (Mathieu-score) and by using quantitative methods.
10. A specific tissue vulnerability has to be assumed for the adult onset form of mild severity. The highly variable or absent correlations of different kinds of organ involvement with the score for neuromuscular deficit (Mathieu), and thus indirectly (CTG)n excess, may support such an assumption.

EPILOGUE

Our study results indicate that MyD quantitative clinical investigations may be essential to discover expression of organ involvement, to assess its severity and to outline its course. Many questions remain unsolved with regards to the variable expressivity, (variation in severity, type of organ involvement and course).

Since we have to deal with mozaisism and unknown cellular effects of the (CTG)n excess, the expressivity should in fact be re-examined for *each organ system* in genetically well defined groups of patients. For example, the visual system is an excellent clinical human model for expression related issues, suitable for all kinds of quantitative measurements. Likewise, the computerized speech analysis and oculomotor studies presented in this thesis are candidates for such studies.

In order to reduce variability in clinical studies, we suggest studying organ specific signs in homogenous groups, (e.g. same age of onset and severity) and using uniform validated quantitative methods.

The main issue to be defined, is how to assess clinically the *extent* and *course* of the disease. In this respect, simple functional but quantitative tests such as the described perioral tests or swallowing tests may be valuable tools for follow up. Furthermore, it is not clear which clinical methods are most appropriate to discover the minimal changes, either for genotype-phenotype correlation studies or for evaluation of future (gene)-therapy or pharmacological modulation.

Given our present knowledge, for each age of onset clinical subgroup with a certain severity, a compilation of studies should be established in order to create an overall picture of the variable expressivity of organ-system involvement.

In the future, the role of the myotonin-proteinkinase gene products and protein phosphorylation processes in mediating the correct protein-protein interactions is expected to be resolved, which may finally result in a proper insight into clinical variability and possible therapeutic opportunities. In advance of this, many basic and (quantitative) clinical investigations will be necessary for well defined groups of MyD patients, before we really understand how the MyD gene and the variable clinical signs are connected.

CHAPTER 6.1

SUMMARY

&

SAMENVATTING

SUMMARY

This thesis presents the results of a serie of clinical studies about the adult onset or 'classical form' of myotonic dystrophy (MyD). After a global introduction about MyD, the aim and outline of the studies have been described, followed by own studies regarding neuro-ophthalmology, neuro-otology, bulbar dysfunction and neuropsychology.

First, in *chapter 1* a selective review of literature has been given, confined to the topics of the several studies.

In *chapter 2.1* the horizontal saccades and smooth pursuit eye movements were studied in 26 patients with myotonic dystrophy. Clinical neuro-ophthalmological investigations in 1 patient revealed an inability to achieve a full range of eye movements. Electro-oculography showed a significant decrease of the maximum velocity of the visually-guided saccades in 83% of the patients. Smooth pursuit eye movements were not significantly different from age-matched controls. Visual evoked potential (VEP) latencies (P100) were significantly prolonged compared with controls in 64% of the patients. The saccadic latency of the visually-guided saccades was correlated with the prolonged VEP latencies, indicating that lesions in the primary visual pathways probably contribute to the oculomotor dysfunction. The isolated decrease of the maximum velocity of the saccades in combination with EMG findings favours a peripheral (dystrophic) pathophysiological mechanism.

Chapter 2.2 deals with eye movement recording (EMR) performed in 5 asymptomatic myotonic dystrophy (MyD) gene carriers, 7 mildly affected MyD patients and 23 age and sex matched healthy controls. The purpose of the study was to evaluate whether eye movement abnormalities are an early expression of the MyD gene and to determine the value of this procedure for detection of otherwise asymptomatic gene carriers. EMR did not reveal any abnormalities in the asymptomatic group, but in the mildly affected group showed significantly ($p<0.01$) decreased maximum velocities of the saccades, compared to controls. The results indicate that EMR may add in the detection of mildly affected MyD patients. However, the use of EMR in preclinical diagnosis of putative MyD gene carriers has no additional value.

Chapter 2.3 A 6 year follow-up study of eye movements was performed in 6 patients with myotonic dystrophy (MyD). In agreement with previous studies the major finding was a symmetrical decrease of maximum velocity of the visually guided saccades (Vmax) with normal latency of the saccades and normal smooth pursuit gain. Deterioration of Vmax ($p<0.01$), weakness of the limbs ($p<0.01$) and VEP P100 latency ($P<0.05$) were significant. We conclude that the oculomotor disturbance in MyD is definitely progressive, correlating

with progression of weakness of the limbs ($p<0.05$). The pattern is in agreement with a predominantly peripheral pathophysiological mechanism.

In *chapter 2.4* twelve subjects with minimal expression of the myotonic dystrophy (MyD) gene were studies and investigated by retinal densitometry, a technique which has been used to study the properties of photopigments in the living eye and to detect photoreceptor abnormalities. Other investigations included slit-lamp examination, fundoscopy, raleigh matches with the anomaloscope, tonometry, and neurological examination, including electroretinography (ERG) and pattern visual evoked potentials recording (pVEP). Foveal densitometry demonstrated reduced values of the macular photopigment density difference with normal photopigment kinetics in early phases of the disease, even in asymptomatic individuals. The densitometric values correlated with decreased amplitudes of the photopic ERG a-wave. These findings may be explained by loss or dysfunction of the outer segments of foveal receptors. It is yet unknown whether or not these changes are secondary to other observed neuro-retinal abnormalities in MyD. The most likely explanation might be an abnormality of the Na, Ca:K exchanger at the level of the outer segments of the photoreceptors whether or not in combination with a dysfunction of voltage generation systems, involving both photoreceptors and RPE.

In *chapter 3* auditory and vestibular tests and oculomotor, were described which were performed in 13 patients with myotonic dystrophy (MyD). All of the 13 patients showed one or more abnormalities. There was a significant increase in the penetrance of separate abnormalities with age. Saccadic slowing was found in 10 patients, in severe form in 3. Seven patients had a sensorineural high-tone hearing loss (30–85 dB at 8Hz), which was in excess of that expected for their age, that could be attributed to MyD. Brain stem auditory-evoked potential;s showed a significant interwave delay of the I-V interval (0.35–0.7 ms). An abnormal vestibulo-ocular reflex was found in 6 patients; 3 had vestibular hyperreflexia with increased gain and 3 hyporeflexia with short time constants. This study confirms that in MyD, sensory system involvement can be found both on a peripheral and a central level.

Chapter 4.1 stressed the importance of a bedside test for swallowing. The objective of the study was to assess the merits of a quantitative bedside test for screening and follow up of swallowing function in myotonic dystrophy (MyD). The design was as follows: 26 MyD patients with adult onset and 28 age matched controls were investigated as follows: a questionnaire for swallowing disturbances, a bulbar and neuromuscular rating scale and a 5-oz swallowing test, which was performed twice. The main result was that a 5-oz water swallowing test (ST) identified 65% (17/26) of the MyD patients to have a prolonged swallowing time. Even in moderate MyD, swallowing dysfunction

may occur. In agreement with previous studies no correlation with clinical dysphagia was found, while in the current study the disturbance in swallowing was positively correlated with the severity of the limb muscle weakness (Mathieu-score). In sum, the 5-oz water swallowing test seems a sensitive screening tool (65%) for identifying those MyD patients in need of more extensive GI studies, or to monitor the course of the disease.

In *chapter 4.2* computerized analysis of standardized speech tests were reported. To a group of 15 mildly affected, early-adult and adult onset MyD-patients a set of speech- and oral-motor tasks was administered in order to specify on a quantitative level the type of dysarthria, and to assess whether their speech-motor system contains apraxic characteristics. As compared to matched control subjects, the MyD patients showed no signs of apraxia of speech, but clearly exhibited a dysarthric profile. It can be concluded that in the speech-motor system of mildly affected MyD patients there is no involvement of speech motor *programming*. The observed speech motor *execution* signs point to flaccid dysarthria and myotonia, particularly in the perioral musculature.

Brain involvement in early and adult onset patients is topic of *chapter 5*. Many studies have revealed intellectual deficits in myotonic dystrophy. However, the groups of patients in these studies were heterogeneous with respect to intelligence, and severity and onset of disease. The present study was undertaken to investigate whether patients with early adult and adult myotonic dystrophy show subtle cognitive deficits despite a normal intelligence. We compared 26 normal intelligent MyD patients with mild symptoms and early adult and adult onset myotonic dystrophy to 25 matched control subjects on a range of neuropsychological tests and a number of motor tasks of increasing complexity, which required increasingly cognitive control. We found hardly any evidence of cognitive dysfunction in our group of myotonic dystrophy patients with early adult and adult onset. The groups did not differ as far as the neuropsychological tests were concerned, with the exception of the Stroop Colour Word Test. With respect to motor performance, the myotonic dystrophy patients were poorer scorers on simple and automatic motor tasks than control subjects, but the difference decreased and eventually disappeared as the complexity of the tasks increased and required correspondingly more cognitive control.

Chapter 6 contains a general discussion about the results of investigations, the summaries and epilogue.

SAMENVATTING

In dit proefschrift worden na een globale introductie over het ziektebeeld myotone dystrophy (MyD), de vraagstelling en het doel van de klinische studies uiteengezet. Achtereenvolgens worden de eigen klinische studies besproken, welke betrekking hebben of neuro-ophthalmologie, neuro-otologie, bulbaire dysfunctie en neuropsychologie.

Alvorens de eigen studies te bespreken, vindt men in *hoofdstuk 1* een toegespitst overzicht van de relevante literatuur.

In *hoofdstuk 2.1* worden de resultaten beschreven van een onderzoek naar de visueel geleide horizontale saccaden en langzame volgbeweging van de oogbewegingen van 26 patiënten lijdende aan dystrofische myotonie. In totaal behoorden 23 tot de 'adult onset' groep. Klinisch onderzoek van de oculomotoriek bracht bij 1 patiënt een beperking van de oogmotiliteit aan het licht. Electro-oculografisch onderzoek liet echter een significante afname zien van de maximum snelheid der saccaden (Vmax.) bij 83% der patiënten. Langzame volgbewegingen verschilden niet ten opzichte van de controles met een overeenkomstige leeftijd. Visuele 'evoked potential' (VEP) studies lieten een verlengde latentietijd der P100 zien bij 64% van de patiënten. De latentie van de visueel geleide saccaden bleek te correleren met de latentie van de P100 van de VEP. Op grond hiervan mag men een lesie veronderstellen van het afferente optisch systeem, welke ook tot uitdrukking komt bij de oogmotoriek. De Vmax. afname zonder overige oogmotoriek-afwijkingen pleit, zeker als we de EMG bevindingen van de externe oogspieren in ogenschouw nemen, voor een perifere oorzaak als verklaring voor de subklinische oogbewegingsstoornissen.

In *hoofdstuk 2.2* wordt nagegaan in hoeverre oogbewegingsregistaties kunnen bijdragen aan vroegdiagnostiek. Daarom werd bij 5 asymptomatische DNA positieve gendragers en 7 licht tot matig aangedane MyD patiënten een oogbewegingsregistratie vervaardigd.
Alle patiënten op een na behoorden tot de 'adult onset' groep. De resultaten werden vergeleken met 23 controles, welke overeenkwamen qua geslacht en leeftijd. De resultaten van de gendragers waren niet afwijkend t.o.v. de controle groep, terwijl de licht en matig aangedane patiënten wel een significant verschil bleken te vertonen ($p<0.01$). Hieruit valt te concluderen dat oogbewegingsregistaties van nut kunnen zijn bij het opsporen licht aangedane dystrofische myotonie patiënten, maar voor opsporing van asymptomatische gendragers blijkt er geen aanvullende waarde te bestaan.

In *hoofdstuk 2.3* wordt een vervolgstudie beschreven bij 6 patiënten behorend tot de 'adult onset' vorm van MyD. Een onderzoek naar oogparameters, ske-

letspierzwakte en een uitvoerig oogbewegingsonderzoek (identiek aan het onderzoek als beschreven in hoofdstuk 2.1) werd herhaald na 6 jaar. De maximum snelheid der saccaden (Vmax) bleek significant te zijn afgenomen, terwijl de langzame volgbewegingen onveranderd bleken te zijn. De achteruitgang van de Vmax. bleek significant te correleren met de resultaten van de ledemaatspieren (Mathieu-rating-scale). Dit veronderstelt eveneens een perifere genese als oorzaak van de afgenomen snelheid der saccaden.

Hoofdstuk 2.4 behandelt de retinale afwijkingen van patiënten met een minimale expressie van het gen voor dystrophische myotonie. De twaalf geselecteerde patiënten behoorden op een na allen tot de 'adult onset' vorm van dystrophische myotonie. Zij werden neurologisch, oogheelkundig onderzocht. Vervolgens werd bij elk van hen een foveale densitometrie vervaardigd, een techniek om de eigenschappen van photopigment in het oog te bestuderen, teneinde afwijkingen van de functie der photoreceptoren te ontdekken. Tevens werd in het onderzoek betrokken een spleetlamp onderzoek, anomaloscoop (kleurenzien) test, oogboldruk metingen, electroretinogram (ERG) en een visueel 'evoked potential' (VEP). Bij het bidirectionele foveale densitometrie onderzoek bleek in 50% er sprake van afwijkingen van de functie der photoreceptoren ten opzichte van controles. De afwijkende bevindingen der foveale densitometrie bleken te correleren met de fotopische a-golf afname van het ERG. Dit ondersteunde onze hypothese van teloor gaan of functie-stoornis van de foveale photoreceptoren. De meest voor de hand liggende verklaring lijkt een stoornis in de Na, Ca:K 'exchanger' op het niveau van de buitenste segmenten van de photoreceptoren, al dan niet in combinatie met een stoornis van de 'voltage generating systems', welke stoornis uiteindelijk zowel de photoreceptoren als het retinale pigment epitheel kan aantasten.

In *hoofdstuk 3* wordt ingegaan op auditieve, vestibulaire en oculomotoriektesten. De vraag is in hoeverre perifeer- en centraal bepaalde mechanismen verantwoordelijk zijn voor de afwijkingen op neuro-otologische terrein. Bij 13 myotone dystrophie patiënten, waarvan 12 'adult onset', werden de bovenbeschreven testen uitgevoerd. Alle patiënten bleken bij een of meerdere testen afwijkingen te vertonen. Met het vorderen der leeftijd bleken de afwijkingen toe te nemen. Bij 10 patiënten werd een vertraging der visuele saccaden gevonden, in ernstige mate bij 3. Zeven patiënten bleken een perceptief hoge tonen verlies te hebben in de orde van 35-80 dB bij 8Hz. De 'brainstem evoked potentials (BAEP)' lieten een verlengd interval tussen top I en V zien. In totaal 6 patiënten bleken afwijkingen te hebben wat betreft de vestibulo-oculaire reflex, 3 vertoonden vestibulaire hyperreflexie met toegenomen 'gain', terwijl er bij de overige 3 patiënten juist hyporeflexie werd gevonden. Deze studie bevestigt dat in dystrophische myotonie dus zowel centraal als perifeer afwijkingen worden gevonden in het sensore neuro-otologische systeem.

In *hoofdstuk 4.1* komen slikstoornissen aan de orde bij dystrophische myotonie (MyD). Met behulp van een simpele en quantitatieve sliktest werden 26 'adult onset' MyD patiënten en 28 controles onderzocht volgens een vast protocol. Bij alle patiënten werd een vragenlijst afgenomen t.a.v. slikklachten en werd de ernst vastgelegd middels een bulbaire- en neuromusculaire rating scale. Ook werd de duur bepaald hoe snel men 150 cc H2O kon slikken (ST). Hieruit bleek dat de tijd benodigd voor het slikken frequent verlengd was (17/26, 65%). Zelfs in deze matig aangedane groep patiënten komen blijkbaar al slikstoornissen voor. In overeenstemming met voorgaande onderzoekingen werd er geen verband aangetoond met de klachten van het slikken en de duur van het slikken. In de huidige studie werd voor het eerst een correlatie aangetoond tussen objectief meetbare functionele slikstoornis (ST) en ernst der spierzwakte. Concluderend, mag men stellen dat de besproken ST een tamelijke sensitief (65%) instrument is voor het opsporen van patiënten met functionele slikstoornisen of om die patiënten te selecteren waarbij aanvullend slikonderzoek aan te bevelen is. Tevens kan het natuurlijk beloop van de slikstoornis op deze manier in kaart worden gebracht.

In *hoofdstuk 4.2* is bij 15 'adult onset' MyD patiënten middels een computer-analyse de spraak en (peri)orale musculatuur onderzocht, teneinde het type dysarthrie nader te onderzoeken en om na te gaan of er sprake is van een programmeringsstoornis der spraak (dyspraxie). Ten opzichte van controles, bleek er geen dyspraxie aantoonbaar. Dientengevolge mag men concluderen dat er bij weinig aangedane adult onset patiënten de programmering der spraak normaal is. De waargenomen stoornis van de spraak pleit voor een slappe (bulbaire) dysarthrie, waarbij in het bijzonder de myotonie in de periorale spieren een belangrijke rol lijkt te spelen.

Hoofdstuk 5 betreft een onderzoek naar cognitieve stoornissen bij een licht tot matig aangedane groep MyD patiënten, welke allen tot de 'adult onset of vroeg adulte' type behoren. Uit veel studies blijkt dat er een intellectuele dysfunctie in het kader van MyD moet worden verondersteld. De bestudeerde groepen patiënten zijn echter vrijwel altijd heterogeen wat betreft intelligentie, ernst of tijdstip van begin der ziekte. De onderhavige studie had ten doel om na te gaan of er subtiele afwijkingen op cognitief terrein konden worden waargenomen bij 26 patiënten met een 'adulte' of 'vroeg adulte vorm' van MyD. In totaal werden 26 patiënten met een normaal IQ bereid gevonden om deel te nemen aan deze studie. De bevindingen werden afgezet tegen die van 25 vergelijkbare controles. Met uitzondering de Stroop Colour Word Test (SCWT) werden er geen significante neuropsychologische afwijkingen gevonden ten opzichte van een controle groep met overeenkomstige leeftijd, geslacht, opleiding en IQ. Ook na correctie voor motoriek bleef de SCWT afwijkend. Wel scoorden de MyD patiënten doorgaans slechter op simpele taken der

handmotoriek. Dit verschil ten opzichte van controles verdween opmerkelijk genoeg bij de complexere handmotoriek opdrachten.

In *hoofdstuk 6* komt de algemene discussie aan de orde naast de samenvattingen van de klinische studies. In het slotwoord worden de lijnen naar toekomstig klinisch onderzoek aangestipt.

REFERENCE LIST

1 Abel L, Schmidt D, Dell'Osso L, Daroff R Saccadic system plasticity in humans Ann Neurol 1978, 4 313-318
2 Adie W, Greenfield J Dystrophia myotonica (myotonia atrophica) Brain 1923, 46 73-127
3 Albert M, Feldman R, Willis A The subcortical dementia of progressive supranuclear palsy J Neurol Neurosurg Psychiatry 1974, 37 121-130
4 Albert M Subcortical dementia In Alzheimer's disease senile dementia and related disorders Aging Katzmann R, Terry R, Bick K eds Raven Press New York 1978, 7
5 Albrecht W Ueber Veranderungen in den oberen Luft und Speisewegen bei Myotonica atrophica Arch Laryngol Rhinol 1920, 33 45
6 Alpern M Lack of uniformity in colour matching J Physiol 1979, 288 85
7 Anvret M, Ahlberg G, Grandell U, Hedberg B, Johnson K, Edstrom L Larger expansions of the CTG repeat in muscle compared to lymfocytes from patients with myotonic dystrophy Hum Mol Genet 1993, 2 9 1397-1400
8 Appel V, Stewart S, Smith G Rating scale for amyotrophic lateral sclerosis description and preliminary experience Ann Neurol 1987, 22 328-333
9 Aram D and Horwitz S Sequential and non-speech praxic abilities in developmental verbal apraxia Develop Med Child Neurol 1983, 25 197-206
10 Aslanidis C, Jansen G, Amemiya C, Shutler G, Mahadevan M, Tsilfidis C, Chen C, Alleman J, Wormskamp NGM, Vooijs M, Buxton J, Johnson K, Smeets HJM, Lennon GG, Carrano AV, Korneluk RG, Wieringa B, de Jong PJ Cloning of the essential myotonic dystrophy region and mapping of the putative defect Nature 1992, 355 548-551
11 Ashizawa T, Hejtmancik J, Liu J, Perryman M, Epstein H, Koch D Diagnostic value of ophthalmological findings in myotonic dystrophy comparision with risks calculated by haplotype analysis of closely linked restriction fragmentlength polymorphisms Am J Med Genet 1992 42 55-60
12 Ashizawa T, Dubel J, Tran L Muscle DNA shows different triplet expansion size from peripheral blood leucocyte DNA in myotonic dystrophy Neurology 1993, 43 A 413 (abstract)
13 Avrahami E, Katz A, Bornstein N, Korczyn A Computed tomography findings of brain and skull in myotonic dystrophy J Neurol Neurosurg Psychiatry 1987, 50 435- 438
14 Babel J, Tsacopoulos M Les lesions retiniennes de la dystrophie myotonique Ann Ocul (Paris) 1970, 203 1049-1065
15 Babel J Ophthalmological aspects of myotonic dystrophy In Neurogenetics and Neuro-ophthalmology Huber and Klein eds Elsevier North Holland Biomedical Press 1981 19-31
16 von Bahr, G Cataract in general disease The Montgomerey Lecture 1967 In Transactions of the ophthalmological Societies of the United Kingdom 1967, 87 811-824
17 Ballantyne J, Hansen S Computer method for analysis of evoked motor unit potentials 2 Duchenne, limb girdle, facioscapulohumeral and myotonic muscular dystrophies J Neurol Neurosurg Psychiatry 1975, 38 417-428
18 Baloh R, Konrad H, Sills A, Honrubia V The saccade velocity test Neurology 1975, 25 1071-1076
19 Bamford K, Caine E, Kido D, Plassche W, Shoulson I Clinical-pathologic correlation in Huntington's disease a neuropsychological and computed tomography study Neurology 1989, 39 796-801
20 Barlow S and Rath E Maximum voluntary closing forces in the upper and lower lips of humans J Speech Hearing Res 1985, 28, 373-376
21 Bartel P, Lotz B, van der Meyden C Short latency somatosensory evoked potentials in dystrophia myotonica J Neurol Neurosurg Psychiatry 1984 47 524-529
22 Barwick D, Osselton J, Walton J Electroencephalographic studies in hereditary myopathy J Neurol Neurosurg Psychiatry 1965, 28 109-114
23 Bastiaensen L Chronic progressive external ophthalmoplegia Thesis Nijmegen NL 1978 19-38

24 Batten F and Gibb H Myotonia atrophica Brain 1909, 32 187
25 Bell J Dystophia myotonica and allied diseases With clinical notes by J Purdon Martin The treasury of human inheritance Cambridge University Press 1947, 4, 5
26 Benders A, Timmermans J, Oosterhof A, ter Laak H, van Kuppeveld T, Wevers R, Veerkamp J Deficiency of Na+/K+-ATPase and sarcoplasmatic reticulum Ca2+-ATPase in skeleteal muscle and cultured muscle cells of myotonic dystrophy patients Biochemistry 1993, 293 269-274
27 Benecke R, Rothwell J, Dick J, Day B, Marsden C Simple and complex movements off and on treatment in patients with Parkinson's disease J Neurol Neurosurg Psychiatry 1991, 50 296-303
28 Berg E A simple objective technique for measuring flexibility of thinking J Genet Psychol 1948, 39, 15-22
29 Berthold H Zuer pathologischen Anatomie der Dystrophia Myotonica (Curshmann-Steinert) Dtsch Z Nervenheilkd 1958, 178 394- 412
30 Bethlem J Dystrophia Myotonica (Ziekte van Steinert) Thesis Amsterdam NL 1955
31 Betten M, Bilchik R, Smith M Pigmentary retinopathy of myotonic dystrophy Am J Ophthalmol 1971, 72 720-723
32 Bird T, Follet C, Griep E Cognitive and personality function in myotonic muscular dystrophy J Neurol Neurosurg Psychiatry 1983, 46 971-980
33 Black W, Ravin A Studies in dystrophia myotonica VII Autopsy observations in five cases Arch Pathol 1947, 44 176-191
34 Blanksma L, Kooijman A, Siertsema J, Roze J Fluoro-photometry in myotonic dystrophy Doc Ophthalmol 1983, 56 111-114
35 Bollen E Oogbewegingen bij dystrofia myotonica Symposium dystrofia myotonica Utrecht NL 1991, 60- 64
36 Bollen E, den Heyer JC, Tolsma M, Van Allen M Eye movements in myotonic dystrophy Brain 1992, 115 445-450
37 Bos J Dynamics of the the human pupillary system Thesis Amsterdam NL 1991
38 Bosma J and Brodie D Cineradiographic demonstration of pharyngeal area myotonia in myotonic dystrophy patients Radiology 1969, 92 104-09
39 Bosma J Progressive motor disabilities of mouth Postgrad Med 1971, 49 162-166
40 Bowen F Behavioral alterations in patients with basal ganglia lesions In The Basal Ganglia Research Publications Association for Research in Nervous and Mental Disease Yahr M ed New York, Raven Press 1976, 55 169-177
41 Bramwell E, Adis W Edingb Med J 1913, 11 21
42 Brandt D, Leeson C Structural differences of fast and slow fibres in human extra-ocular muscles Am J Ophthalmol 1966, 62 478-487
43 British Medical Research Council Aid to the investigation of peripheral nerve injuries, 2nd Ed London, England, Her Majesty's Stationary Office, 1943/1982
44 Brook J, McCurach M, Harley H, Buckler A, Church D, Aburatani H, Hunter K, Stanton V, Thirion J, Hudson T, Sohn R, Zemelman B, Snell RG, Rundle SA, Crow S, Davies J, Shellbourne P, Buxton J, Jones C, Juvonen V, Johnson K, Harper P, Shaw D, Housman D Molecular basis of myotonic dystrophy expansion of a trinucleotide (CTG) repeat at the 3' end of a transcript encoding a protein kinase family member Cell 1992, 68 799-808
45 Brooke M A clinician's view of neuromuscular diseases Baltimore, Williams & Wilkens eds 1986, 194
46 Broughton R, Stuss D, Kates M, Roberts J, Dunham W Neuropsychological deficits in sleep in myotonic dystrophy Can J Neurol Sci 1990, 17 4 410-415
47 Brown R, Marsden C Internal versus external cues and the control of attention in Parkinson's disease Brain 1988, 111 323-345
48 Brown R, Marsden C Dual task performance and processing resources in normal subjects and patients with Parkinson's disease Brain 1991, 114 215-231

49. Brumback R. Disturbed personality and psychosocial adjustment in myotonic dystrophy. relationship to intellectual/cognitive function and underlying affective disorder (depression). Psychol Rep 1987; 60: 783-796.
50. Brumback R Magnetic resonance imaging and clinical correlates of intellectual impairment in myotonic dystrophy. Arch Neurol 1990; 47· 253-254
51. Brunner H, Coerwinkel-Driessen M, Smeets B, Schonk D, Schepens J, Oerlemans F, Hamel B, Ropers HH, Wieringa B. Definition of subchromosomal intervals around the myotonic dystrophy locus at 19q. In: Genetics of neuromuscular disorders. Bartsocas C ed. A R Liss Inc. New York 1989a: 107-114.
52. Brunner H, Smeets H, Lambermon H, Coerwinkel-Driessen M, van Oost B, Wieringa B, Ropers H. A multipoint linkage map around the locus for myotonic dystrophy on chromosome 19. Genomics 1989b; 5: 589-595.
53 Brunner H, Smeets H, Nillesen W, van Oost B, Biezenbosch J, Joosten E, Pinckers A, Hamel B, Theeuwes A, Ropers H. Myotonic dystrophy: predictive value of normal results on clinical examination. Brain; 1991; 114: 2303-2311.
54. Brunner H, Nillesen W, van Oost A, Jansen G, Wieringa B, Ropers H, Smeets H Presymptomatic diagnosis of myotonic dystrophy. J Med Genet 1992a; 29: 780-784.
55. Brunner H, Hamel B, Rieu P, Howeler C, Peters F. Intestinal pseudo-obstruction in myotonic dystrophy. J Med Genet 1992b: 29· 791-793
56. Brunner H, Jansen G, Nillesen W, Nelen M, de Die C, Höweler C, van Oost B, Wieringa B, Ropers H, Smeets H. Reverse mutation in myotonic dystrophy New Engl J Med 1993a; 328: 476-480
57. Brunner H. Genetic studies in Myotonic Dystrophy. Thesis. Nijmegen NL 1993.
58. ter Bruggen J, Bastiaensen L, Tijssen C, Gielen G. Disorders of eye movement in myotonic dystrophy Brain 1990; 113· 463-473.
59. ter Bruggen J, Tijssen C, Brunner H, van Oost B, Bastiaensen L. Eye movement disorder· an early sign of expression of the myotonic dystrophy gene? Muscle Nerve 1992a; 15: 358-361.
60. ter Bruggen J, van Meel G, Parıdaens A, Tijssen C, van Norren D. Foveal photopigment kinetics- abnormality: an early sign in myotonic dystrophy? Br J Ophthalmol 1992b; 76: 594-597.
61. ter Bruggen J, Tijssen C, Bastiaensen L. Myotonic dystrophy: the natural history of eye movement disorders. Neuro-Ophthalmol 1993: 13: 2: 85-88.
62. Bundey S, Carter W. Genetic heterogenity for dystrophia myotonica J Med Genet 1972; 9: 311-315.
63. Bundey S. Detection of heterozygotes for myotonic dystrophy. J Med Genet 1974; 19: 5: 107-109.
64 Bundey S. Detection of heterozygotes for myotonic dystrophy. Clin Genet 1982; 19: 341-348.
65. Bundey S. Genetics and neurology. Churchill Livingstone, Edinburgh 1985.
66. Burian H and Burns C. Electroretinography and dark adaptation in patients with myotonic dystrophy. Am J Ophthalmol 1966; 61: 1044.
67. Burian H and Burns C. Ocular changes in myotonic dystrophy. Am J Ophthalmol 1967; 63: 22.
68. Burns C Ocular histopathology of myotonic dystrophy. Am J Ophthalmol 1969; 68: 416-422
69. Buschke W. Dystrophic cataract and their relation to other 'metabolic' cataracts. Arch Ophthalmol 1943; 30: 751-762.
70. Buxton J, Shelbourne P, Davies J, Jones J, van Tongeren T, Aslanidis C, de Jong P, Jansen G, Anvret N, Riley B, Williamson R, Johnson K. Detection of an unstable fragment of DNA specific to individuals with myotonic dystrophy. Nature; 1992, 355: 547-548.
71. Buytenhuys E, Berger H, van Spaendonck K, Horstinck M, Borm G, Cools A. Memory and learning in patients with Parkinson's disease Neuropsychologica (in press)
72. Caccia M, Negri S, Preto Parvis V. Myotonic dystrophy with neural involvement. J Neurol Sci 1972; 16· 253-269.

73. Caine E, Fisher J. Dementia in Huntington's disease. In: Handbook of Clinical Neurology. Neurobiological Disorders. Frederiks J ed. Amsterdam: Elseviers Science Publishers 1985; 2.
74. Calderon R. Myotonic dystrophy: a neglected cause of mental retardation. J Pediatr 1966; 68: 423-431.
75. Calvet J, Coll J, Dussert J. Scientific report from the 27th congress: speech disorders in peripheral neurologic disorders. J Fr Otorhinolaryngol 1970; 19: 7: 539-553.
76. Camilleri M. Disorders of gastro-intestinal motility in neurogenic diseases. Mayo Clin Proc 1990; 65: 825-846.
77. Carosio J, Cohen J, Zawodniak J. A double blind placebo controlled trial of TRH in amyotrophic lateral sclerosis. Neurology 1986, 36: 141-145.
78. Caughy J and Myrianthoupolos N Dystrophia Myotonica and related disordrs. Springfield, III· Thomas C ed. 1963.
79. Celesia C. Steady state and transient visual evoked potentials in clinical practice. Ann NY Acad Sci 1982; 388: 290.
80. Celesia C, Cone S. Visual evoked potentials: a practical approach within the guidelines for clinical evoked potential studies. Am J EEG Technol 1985; 25: 93.
81. Censori B, Danni M, Del-Pesce M, Provinciali L. Neuropsychological profile in myotonic dystrophy. J Neurol 1990: 237: 251-256.
82. Chang L, Anderson T, Migneco A, Boone K, Mehringer M, Villanueva-Meyer J, Berman N, mena I. Cerebral abnormalities in myotonic dystrophy: cerebral blood flow, magnetic resonance imaging and neuro- psychological tests. Arch Neurol 1993; 50: 917-923.
83. Chiu V and Englert E. Gastrointestinal disturbances in myotonica dystrophica. Gastroenterology 1962; 42: 745-746 (abstr)
84. Cobo A, Baiger M, Lopez de Munain A Sex related differencin intergenerational expansion in myotonic dystrophy. Lancet 1993; 431: 1159-1160.
85. Coers C. La dystrophie myotonique Acta Clin Belg 1952; 7: 407-444
86 McComas A, Campbell M, Sica R. Electrophysiological study of dystrophia myotonica. J Neurol Neurosurg Psychiatry 1971; 34: 132-139.
87. Cook J, Glass D. Strength evaluation in neuromuscular disease. Neurologic Clinics 1987; 5: 118.
88. Cools A, van den Bercken J, Horstink M, van Spaendonck K, Berger H Cognitive and motor shifting aptitude disorder in Parkinson's disease. J Neurol Neurosurg Psychiatry 1984, 47:443-453.
89. Creel D, Crandall A, Ziter F. Identification of minimal expression of myotonic dystrophy using electroretinography. Electroenceph Clin Neurophysiol 1985; 61: 229-235.
90. Culebras A, Feldman R, Merk F Cytoplasmic inclusion bodies within neurons of the thalamus in myotonic dystrophy. J Neurol Sci 1973, 19. 319-329.
91. Cummings J, Benson D. Subcortical dementia: a review of an emerging concept. Arch Neurol 1984; 41· 874-879
92. Cummings J. The dementias of Parkinson's disease: prevalence, characteristics, neurobiology, and comparison with dementia of the Alzheimer type. Eur Neurol 1988; 28; 1: 15-23 (suppl).
93. Curshmann H. Ueber familiare atrophische Myotonie Dtsch Z Nervenheilkd 1912: 45: 161-202.
94. Curshmann H. Zur Nosologie und SAymptomatologie er myotonischer Dystrophie. Dtsch Arch Klin Med 1925; 149-144.
95. Curshmann H. In. Myotonische Dystrophie. Handbuch der Neurologie. Bumke and Forster eds Springer Verlag 1936· 465
96. Cuthill J, Gatereau A, Vigue F. Myotonic dystrophy of Steinert: are anxiety and depression necessary concomitants? Can J Psychiat 1988; 33: 203-206
97. Cyr J, Brooker B Use of appropriate formulas for selecting WAIS-R short forms J Consult Clin Psychol 1984; 52: 903-905
98 Damian M, Bachmann G, Hermann D, Dorndorf W. Magnetic resonance imaging of muscle and brain in myotonic dystrophy. J Neurol 1993; 240 8-12

99 Dana C An atypical case of Thomsen's disease (myotonia congenita) Med Rec New York 1888, 33 433

100 Dark A and Streeten B Ultrastructural study of cataract in myotonia dystrophica Am J Ophthalmol 1977, 84 666-674

101 Darley F, Aronson A, Brown J Motor speech disorders WB Saunders Philadelphia/-London/Toronto, 1975

102 Davidson S The eye in dystrophia myotonica Br J Ophthalmol 1961, 45 183-196

103 Delis D, Kramer J, Kaplan E, Ober B The California Verbal Learning Test Research edition New York The Psychological Corporation 1978

104 McDermot V The histology of the neuromuscular junction in dystrophia mytonica Brain 1962 75-84

105 Desnuelle C, Lombert A, Serratric G, Lazdunski M Sodium channel and sodium pump in normal and pathological muscles from patients with myotonic dystrophy and lower motor neuron impairment J Clin Invest 1982, 69 358-367

106 Deutman A The Craig lecture Genetically determined retinal and choroideal disease Trans Ophthalmol Soc UK 1974, 94 1014-1032

107 Dewey D, Roy E, Square-Storer P, Hayden D Limb and oral praxic abilities of children with verbal sequencing deficits Develop Med Child Neurol 1988, 30 743-751

108 Dietert S The demonstration of different types of muscle fibers in human extra-ocular muscle by electron microscope and cholinesterase staining Invest Ophthalmol 1965, 4 51-63

109 Dowling J The Retina an approachable part of the brain The Belknap press of Harvard University 1967 Dreyer R Ocular hypotonia in myotonic dystrophy Int Ophthalmol 1983 6 221-223

110 Duke-Elder S System of Ophthalmology Kimpton London 1969, 10 186-187

111 Dunne F Subcortical dementia BMJ 1993, 307 1-2

112 Duveneck M, Portwood M, Wicks J, Lieberman J Depression in myotonic muscular dystrophy Arch Phys Med Rehabil 1986, 67 875-877

113 Dyer F The Stroop phenomenon and its use in the study of perceptual, cognitive, and response processes Memory Cognition 1973, 1 106-120

114 Dyken P Extra-ocular myotonia in families with dystrophia myotonica Neurology 1967, 16 738-740

115 Dijken P The changing syndromes of dystrophia myotonica Neurology 1969, 19 292

116 Dijken P, Harper P Congenital dystrophia myotonica Neurology, 23 465-473

117 Eckel F and Boone D (1981) The s/z ratio as an indicator of laryngeal pathology J Speech Hear Dis 1981, 46 147-149

118 Eckhart V, Nix W, Kraus W, Bohl J Esophageal motor function in patients with muscular dystrophy Gastroenterology 1986, 90 628-635

119 Eckhart V and Nix W The anal sphincter in patients with myotonic muscular dystrophy Gastroenterology 1991, 100 424-430

120 Eiberg H, Mohr J, Niehlsen L, Simonsen N Genetic and linkage relationships of the C3 polymorfism discovery of the C3 Se linkage and assignment of LES-C3-DM-Se-PEPD-LU synteny to chromosome 19 Clin Genet 1983, 24 159-170

121 Emery A Population frequencies of inhereted neuromuscular diseases-a world survey Neuromuscular Disorders 1991, 1, 1 19-29

122 Emre M and Henn V Central eye movement disorder in a case of myotonic dystrophy Neuro-Ophthalmol 1985, 5 21-25

123 Eshaghian J, March W, Goossens W, Rafferty N Ultrastructure of cataract in myotonic dystrophy Invest Ophthalmol Vis Sci 1978, 17 239-293

124 Faber D Analysis of the slow transretinal potentials in response to light Thesis University of New York, Buffalo, 1969

125 Fiorelli M, Mazoyer B, Blin J, Eymard B, Fareau M, Samaon Y Decreased cerebral glucose utilization in myotonic dystrophy Neurology 1992, 42 91-94

126. Fleisher B. Ueber myotonische Dystrophie mit Katarakt. Albrecht von Graefes. Arch Klin Ophthalmol 1918; 96. 91-133.
127. Fletcher A. Time-by-count measurement of diadochokinetic syllable rate. J Speech Hear Res 1972; 15: 763-770.
128. Franceschetti A, Francois J, Babel J. Degenerescene tapeto-retinienne et dystrophie myotonique (maladie de Steinert). In: les heredo-degenerescences choreo-retiniennes (degenerescences tapeto-retiniennes) Paris Masson 1963; 2: 1079-1084.
129. Franzese A, Antonini G, Ianelli M, Leardi M, Spada S, Vichi R. Intellectual functions and personality in subjects with noncongenital myotonic muscular dystrophy. Psych Rep 1992; 68: 723-732.
130. Fridlund A, Delis D. The California Verbal Learning Test, scoring and administration software. New York: The Psychological Corporation 1987.
131. Fu Y, Pizutti A, Fenwick R, King J, Rajnarayan S, Dunne P, Dubel J, Nasser G, Ashizawa T, de Jong P, Wieringa B, Korneluk R, Perryman M, Epstein H, Caskey C. An unstable triplet repeat in a gene related to myotonic dystrophy. Science 1992:1256-1258.
132. Fu Y, Friedman D, Richards S. Varying expression of myotonin-protein kinase mRNA and protein levels in the adult form of myotonic dystrophy. Science 1993; 72: 971-983.
133. Gallmore R, Griff E, Hughes B, Steinberg R. Evidence in support of a photoreceptor origin for the 'light-peak substance'. Invest Ophthalmol Vis Sci 1988; 29· 566-571.
134. Ganes T, Kerty E. Multimodal evoked potentials, EEG and electroretinography in patients with dystrophia myotonica Acta Neurol Scand 1988; 78: 436- 442.
135. Gardner M, Altman D. Confidence intervals rather than P-values: estimation rather than hypothesis. BMJ 1986; 292: 746-750.
136. Gardliner D Behandeling van oro-myofunctionele problemen Een diagnostisch model voor de logopedist. Logopedie en Foniatrie 1987; 59: 80-84.
137. Geurts A, Mulder T, Nienhuis B, Eng M, Rijken R. Dual-task assessment of reorganization of postural control in persons with lower limb amputation. Arch Phys Med Rehabil 1991; 72: 1059-1064
138. Ginsberg J, Hamblet J, Manefee M. Ocular abnormalities in myotonic dystrophy. Ann Ophthalmol 1978; 10: 1021-1028.
139. Glantz RH., Wright RB, Huckman MS, Garron DC, Siegel IM. Central nervous system magnetic resonance imaging findings in myotonic dystrophy. Arch Neurol 1988; 45: 36-37.
140. Goldmann H and Schmidt T. The intraocular pressure. Ophthalmologica 1957; 134: 221-242.
141. Gordon C, Hewer R, Wade DT. Dysphagia in acute stroke. BMJ 1987; 295: 411-414.
142. Gottfredsen E. Concurrence of dystrophia myotonica and dystrophia pigmentosa retinae. Acta Psych Scand 1949; 24: 435-441.
143. Gott P, Karnaze D, Keane J. Abnormal visual evoked potentials in myotonic dystrophy. Neurology 1983; 3· 1622-1625.
144. Greenberg G, Watson R, Deptula D. Neuropsychological dysfunction in sleep apnea. Sleep 1987; 10: 254- 262
145. Griggs R and the working group on molecular defect in myotonic dystrophy. Criteria for establishing the validity in myotonic dystrophy Neurology 1989; 39: 420-421.
146. Griggs R, Jozefowicz R, Kingston W, Sreekumaran N, Her B, Halliday D. Mechanism of muscle wasting in myotonic dystrophy. Ann Neurol 1990; 27: 505-512
147. Hageman A, Gabreèls F, Liem K, Boon J. Congenital myotonic dystrophy; a report on thirteen cases and a review of the literature. J Neurol Sci 1993; 115· 95-101.
148. Halliday D, Ford G, Rennie M Extent of protein synthesis in muscle in myotonic dystrophy. Ann Neurol 1985; 17: 65-69
149. Harley H, Rundle S, Reardon R, Myring J, Crow S, Brook J, Harper P, Shaw D. Unstable DNA sequence in myotonic dystrophy. Lancet 1992; 339: 1125-1128.
150 Harley H, Rundle S, MacMillan J, Myring J, Brook J, Crow S, Reardon W, Fenton I, Shaw D, Harper P Size of the unstable CTG repeat sequence in relation to phenotype and parental transmission in myotonic dystrophy. Am J Hum Genet 1993; 52: 1164-1174.

151 Harper P Genetic studies in myotonic dystrophy Thesis Oxford UK 1972a
152 Harper P and Dyken P Early onset dystrophia myotonia evidence of supporting a maternal environmental factor Lancet 1972b, 2 53-55
153 Harper P Congenital myotonic dystrophy in Britain Genetic aspects Arch Dis Child 1975, 50 514-521
154 Harper P Myotonic dystrophy first edition WB Saunders comp London 1979
155 Harper P Myotonic dystrophy sec edition WB Saunders comp London 1989
156 Harrington D, Haaland K Sequencing in Parkinson's disease Abnormalities in programming and controlling movement Brain 1991, 114 99-115
157 Harris J and Cottam P Phonetic Features and Phonological features in speech assessment British J Dis Com 1985, 20 61-74
158 Hayasaka S, Kioyosawa M, Katsumata S, Honda M, Takase S, Mizuno K Ciliary and retinal changes in myotonic dystrophy Arch Ophthalmol 1984, 102 88-93
159 Heine L Ueber Tetanie-und myotonie-Katarakt Z Augenheilk 1925, 55 1
160 den Heyer J, van Dijk G, Bollen E, Bos J, Wintzen A Assessment of autonomic function in myotonic dystrophy J Neurol Neurosurg Psychiatry 1991, 54 531-534
161 Hess A, Pilar G Slow fibres in the extra-ocular muscles of the cat J Physiol 1963, 169 780-798
162 van Hilten J, Kerkhof G, Dyk van G, Dunnewold R, Wintzen A Disruption of sleep-wake rhytmicity and daytime sleepiness in myotonic dystrophy J Neurol Sci 1993, 114 68-75
163 Howeler C A clinical and genetic study in myotonic dystrophy Thesis Witschiers BV Oss 1986
164 Howeler C, Bush H, Geraeds J, Niermeyer M, Staal A Anticipation in myotonic dystrophy fact of fiction? Brain 1989, 12 779-797
165 Hoogenraad T, Jennekens F, Tan K Histochemical fibertypes in human extra-ocular muscles, an investigation of the inferior oblique muscle Acta Neuropathol 1979, 45 73-78
166 Hoogenraad T Over uitwendige oogspieren microscopische en klinische studies Thesis Utrecht NL 1982
167 Horowitz M, Maddox A, Maddern G, Wishart J, Shearman D Gastric and esophageal emptying in dystrophia myotonica effect of meclopramide Gastroenterology 1987a, 92 570-577
168 Horowitz M, Maddox A, Wishart J, Collins P, Shearman D Alimentary tract and pancreas Effects of cisapride on gastric emptying in dystrophia myotonica J Gastroenterol Hepatol 1987b, 2 285- 293
169 Horvath A Untersuchungen und Ergebnisse ueber Cataracta Myotonica Klin Monatsbl Augenheilk 1973, 163 86-91
170 Houber J and Babel J Les lésions uvéo-rétiniennes de la dystrophie myotonique Etude histologique Ann Ocul 1970, 203 1067-1076
171 Huber S, Kissel J, Shuttleworth E, Chakeres D, Clapp L, Brogan M Magnetic resonance imaging and clinical correlates of intellectual impairment in myotonic dystrophy Arch Neurol 1989, 46 536-540
172 Hull K, Roses A Stoichometry of sodium and potassium transport in erythrocytes from patients with myotonic dystrophy J Physiol 1976, 254 169-181
173 Hunter T Protein kinase classification Meth Enzymol 1991, 200 3-37
174 Hunter A, Tsifildis C, Mettler G, Jacob P, Mahadevan M, Surth L, Korneluk R The correlation of age of onset with CTG trinucleotide repeat amplification in myotonic dystrophy J Med Genet 1992, 29 774- 779
175 Huygen P Nystagmometry the art of measuring nystagmus parameters by digital signal processing ORL 1979, 41 206-220
176 Huygen P Vestibular hyperreactivity in patients with multiple sclerosis Adv Otorhinolaryngol 1983, 30 141-149
177 Huygen P, Nicolasen M Diagnostic value of velocity-stepresponses ORL 1985, 47 249-261

178. Huygen P, Verhagen W, van Hoof J, Horstink M. Vestibular hyperreactivity in patients with idiopathic spasmodic torticollis. J Neurol Neurosurg Psychiatry 1989; 52: 782-785.
179. Huygen P, Verhagen W, Hommes O, Nicolasen M. Short vestibulo-ocular reflex time constants associated with oculomotor pathology in multiple sclerosis. Acta Otolaryngol 1990; 109: 25-33.
180. Interactive Laboratory System V 6.1 (ILS). Goleta, CA: Signal Technology, Inc. 1989.
181. Isashiki Y, Kawabata E, Ohba N, Higuchi I, Nakagawa M, Osame M. Mitochondrial abnormalities in extra-ocular muscles in myotonic dystrophy. Neuro-Ophthalmol 1989; 2: 2: 115-122.
182. ISO 8253-1. Acoustics - Audiometric test methods - Part 1: Basic pure tone air and bone conduction threshold audiometry Geneva, International Organization for Standardization, 1989.
183 ISO 7029. Acoustics - Threshold of hearing by air conduction as a function of age and sex for otologi cally normal persons Geneva, International Organization for Standardization, 1984.
184. Jansen C, Jennekens F, Wokke J, Leppink G, Wijnne H. Liplength and snout indices· methods for quantitative assessment of peri-oral facial muscle strength. J Neurol Sci 1990; 97: 133- 142.
185. Janssen G, Mahadevan M, Amemiya C, Wormskamp N, Segers B, Hendriks W, O-Hoy K, Baird S, Sabourin L, Lennon G, Jap P, Iles D, Coerwinkel M, Hofker M, Carrano H, de Jong P, Korneluk R, Wieringa B. Characterization of the myotonic dystrophy region predicts multiple protein isoform-encoding mRNAs. Nature Genet 1992; 1: 261-266.
186. Janssen G, Wilems P, Coerwinkel M, Nillesen W, Smeets H, Vits L, Höweler C, Brunner H, Wieringa B. Gonosomal mosaicism in myotonic dystrophy patients: involvement of mitotic events in (CTG)n repeat variation and selection against extreme expansion in sperm. Am J Hum Genet 1994; 54 ; 575-585.
187. Jamal G, Weir IW, Hansen S, Ballantyne J. Myotonic dystrophy. A reassessment by conventional techniques and more recently introduced neurophysiological techniques. Brain 1986; 109: 1279-1296.
188. Jennekens-Schinkel A. Cognitie en affect. In: symposium dystrophia myotonica, Utrecht 1991: 43-48.
189. Jensen A, Rohwer W. The Stroop Colour-Word Test: a review. Acta Psychol 1966; 25: 36-93.
190. Jerusalem F, Freshman J. Comparision of treatment trials in ALS between thyreotropin releasing hormaone (TRH) and TRH derivate orotyl-L- histidyl- prolineamide. J Neurol (suppl) 1985; 232: 35.
191. Johnson E, McKenzie S. Kinematic pharyngeal transit times in myopathy: evaluation for dysphagia. Dysphagia 1993; 8: 35-40.
192. de Jong J. Dystrophia myotonica, paramyotonia and myotonica congenita. Thesis. Utrecht NL 1955.
193. de Jong P. Oogafwijkingen bij dystrophia myotonica: hoe specifiek zijn zij? Symposium dystrophia myotonica Utrecht NL 1991: 36-40.
194. Junge J. Ocular changes in dystrophia myotonica, paramyotonica and myotonica congenita. Thesis. Doc Ophthalmol 1966; 21: 1-115.
195. Karagan N, Sorensen J. Intellectual functionning in non-Duchenne muscular dystrophy. Neurology 1981; 31: 448-452.
196. Kato T. Ueber histologische Untersuchungen der Augenmuskeln von Menschen und Saugetieren. Okajimas Folia Anat Jpn 1938; 16: 131-145.
197. Kent R, Rosenbek J. Prosodic disturbances and neurologic lesion. Brain Language 1982; 15:259-291.
198 Kent R, Kent J, Rosenbeck J Maximum performance tests of speech production. J Speech Hear Dis 1982; 52: 367-387.
199. Kerty E and Ganes T. Clinical and electrophysiological abnormalities in the visual system in Myotonic Dystrophy. Ophthalmologica 1989; 198: 95-102.

200 Ketelsen U and Schmidt D Augensymptome und electronenmicroscopische Befinde des M orbicularis oculi bei dystrophischer Myotonie (Curshmann-Steinert) Graef Arch Clin Ophthalmol Exp 1972, 185 245-268

201 Kirkham T, Coupland S Myotonic Dystrophy normal electroretinal function associated with visual evoked potentials abnormalities Neurogenet Neurophthalmol Amsterdam, Elsevier 1981 51-58

202 Kiuchi A, Otsuda N, Nambda Y, Nakano I, Tomonaga M Presenile appaerance of abundant Alzheimer neurofibrillary tangles without senile plaques in the brain in myotonic dystrophy Acta Neuropathol 1991, 82 82 1-5

203 Klein D La dystrophie myotonique (Steinert) et la dystrophie congenitale (Thomsen) en Suisse J Gen Hum 1958, 1 1-328 (suppl)

204 Klich R, Ireland J, Weidner W Articulatory and phonological aspects of consonant substitutions in apraxia of speech Cortex 1979, 15 451-470

205 Koch M, Grimm T, Harley H, Harper P Genetic risks for children of women with myotonic dystrophy Am J Hum Genet 1991, 48 1084-1091

206 Kommerell G, Olivier D, Theopold H Adaptive programming of phasic and tonic components in saccadic eye movements Investigations in patients with abducens palsy Invest Ophthalmol 1976, 15 657-660

207 Korneluk R, MacKenzie A, Nakamara Y, Jacob P, Hunter A A reordering of chromosome 19 long arm DNA markers and identification of markers flanking the myotonic dystrophy locus Genomics 1989, 5 596- 604

208 Kuhn E, Fiehn W Adult form of myotonic dystrophy In Neurogenetics and Neuro-ophthalmology, Huber A and Klein D eds Amsterdam, Elsevier/North-Holland 1981 31-49

209 Kuhn E, Ey W Innenohr schwerhorigkeit bei dystrophia myotonica und dystrophia muscularis progressiva Dtsch Med Wochenschr 1966, 90 947-951

210 Kuroda S, Ihara Y, Nambda R Neurofibrillary changes in the brains of two siblings with myotonic muscular dystrophy Neuropathol (Sendai) 1988, 2 43-48

211 Lavedan C, Hoffman-Radvanyi H, Rabes J, Roume J, Junien C Different sex/dependent constraints in CTG length variation as explanation for congenital myotonic dystrophy Lancet 1993, 341 237

212 Leigh R, Zee D The Neurology of Eye Movements Davis F ed Philadelphia 1983

213 Lessel S, Coppeto J, Samet S Ophthalmoplegia in myotonic dystrophy Am J Ophthalmol 1971, 71 1231- 1235

214 Levasseur M, Baron JC, Legault-Demare F, Pappata S, Maugiere F, Benoit N, Tran Dingh S, Degos DJ, Laplane D, Mazoyer D Brain energy metabolsim in bilateral thalamic infarcts Brain 1992, 115 III 795-807

215 Lezak M Neuropsychological assessment New York, Oxford Oxford University Press, 1983 Logical international phonetics program V 1 40 (LIPP) Miami, FL intelligent hearing systems 1991

216 Lohlein W Frue katarakt bei atrophischer Myotonie Klin Monatbl Augenheilkd 1914, 52 453

217 Lohmann H De test en de praktijk In symposium dystrophia myotonica, Utrecht NL 1991 48-52

218 Longstaff S, Curtis D, Quick J, Talbot J Genetic counseling for myotonic dystrophy a comparision of lens examination and DNA linkage studies Eye 1991, 5 93-98

219 Lugaresi E, Medori R, Montagna P Fatal familial insomnia and dysautonomia with selective degeneration of the thalamic nuclei N Engl J Med 1986, 315 997-1003

220 Lundervold A, Refsum S, Jacobsen W (1969) The EEG in dystrophia myotonica European Neurol, 2, 279- 284

221 Maas O and Paterson A Mental changes in families affected by Dystrophia myotonica Lancet 1937, 232 21

222 Maassen B, Thoonen G, Wit J Towards assessment of articulo-motoric processing capacities in children In Peters HFM, Hulstijn W and Starkweather CW eds Speech Motor Control Stuttering 1991a 461-469 Amsterdam Excerpta Medica 1991a 461-469

223 Maassen B, Thoonen G, Wit J Maximum Performance Tests to Diagnose Neurogenic Speech Disorders in Children ASHA-convention Program 1991b 33 105

224 Maassen B, Thoonen G Consonant production in children with developmental verbal dyspraxia In Leahy M ed, Proceedings of the Interdisciplinary Conference on Speech Language Pathol, Dublin 1993, 7-11 september 1993, 179-186

225 Mahadevan M, Tsilfidis C, Sabourin L, Shutler G, Amemiya C, Jansen G, Neville C, Narang M, Barcelo J, O'Hoy K, Leblond S, Earle-Macdonald J, de Jong P, Wieringa B, Korneluk R Myotonic dystrophy mutation an unstable CTG repeat in the 3' untranslated region of the gene Science 1992 1253- 1256

226 Malloy P, Mishra S, Adler S Neuropsychological deficits in myotonic muscular dystrophy J Neurol Neurosurg Psychiatry 1990, 53 1011-1013

227 Maniecka-Aleksandrowicz B Voice and speech disorders as first symptoms of myotonic dystrophy Otolaryngol Pol 1969, 23 2 243-245

228 Manschot W Histological findings in a case of dystrophia myotonica Ophthalmologica 1968, 155 294- 296

229 Mathieu J, de Braekeleer M, Prevost C, Boily C Myotonic dystrophy clinical assessment of muscular disability in an isolated population with presumed homogenous mutation Neurology 1992, 42 203-208

230 van der Meché F, Bogaard J, van den Berg B treatment of hypersomnolence in myotonic dystrophy with a CNS stimulant Muscle and Nerve 1986, 9 341-344

231 van der Meché F Ademhaling en hypersomnolentie in dystrophia myotonica Symposium dystrophia myotonica Utrecht NL 1991 56-60

232 van der Meché F, Bogaard J, Sluys van der J, Schimsheimer R, Ververs C, Busch H Daytime sleep in myotonic dystrophy is not caused by sleep apnoea (in press)

233 van Meel G, Smith V, Pokorny J, van Norren D Foveal densitometry in serous choroidopathy Am J of Ophthalmol 1986, 102 353-362

234 Medical Research Council Aids to the investigation of peripheral nerve injuries War Memorandum (rev 2nd ed) London HMSO 1943 11-46

235 Messina C, Tonali P, Scopetta C The lack of deep reflexes in myotonic dystrophy a neurophysiological study J Neurol Sci 1976, 30 303-311

236 Mettler P, MacKenzie A, MacLeod H, Lahey D, Hunter A, Korneluk R Electromyogram Clin Neurophysiol Clinical findings in a population at risk for myotonic dystrophy Am J Human Genet suppl 1990, 47, 9 228

237 Meyer R, Navon D, Auslender I, Zonis S Myotonic dystrophy pathological studies of the eyes Ophthalmologica 1980, 181 215-220

238 Mielke R, Herholz K, Fink G, Ritter D, Heiss WD Positron emission tomography in myotonic dystrophy Psych Res Neuroimaging 1993, 50 93-99

239 Milberg W, Albert M Cognitive differences between patients with progressive supranuclear palsy and Alzheimer's disease J Clin Exp Neuropsychol 1989, 11 605-614

240 Miller R and Dowling J Intracellular responses of the Mueller (glial) cells of mudpuppy retina their relation to b-wave of the electroretinogram J Neurophysiol 1970, 33 323-341

241 Miller N (ed) Walsh and Hoyt's Clinical Neuro-Ophthalmology, 4th edition Baltimore Williams and Wilkins, 1985, 2 562-566 and 795-803

242 Mitake S, Nokura K, Inagaki T, Maeda K, Yamamoto T, Niimi T, Shirai T Two autopsy cases of myotonic dystrophy-on the senile changes of the brain Neuropathol (Sendai) 1987, 8 183-184

243 Moxley R Myotonic muscular dystropy In Handbook of Clinical Neurology, Myopathies Rowland LP and DiMauro S eds Elsevier Science Publ NL 1992, 62 209-259

244 Mueller P, Larson G, Summers P S/Z Ratio Variability in Normal Children and Adults Texas J Audiol Speech Pathol 1991, 17 2 43-45

245. Mulder T. A process-oriented model of human motor behavior. toward a theory-based rehabilitation approach. Phys Ther 1991; 71: 157-164.
246. Mulley J, Staples A, Donneley A. Explanation for exclusive maternal origin for congenital form of myotonic dystrophy. Lancet 1993; 341 : 236-237.
247. Newman E. Regulation of potassium levels by glial cells in the retina. TINS 1985: 156-159.
248. Nonne. Combination von Myotonie und Dystrophia Muscularis. Neurol Centralb 1905: 142.
249. von Noorden G, Thompson H, Van Allen M. Eye movements in myotonic dystrophy: an electro-oculographic study. Invest Ophthalmol 1964; 3: 314-324.
250. Norman D, Shallice T. Attention to action. Willed and automatic control of behavior. In: Consciousness and selfregulation. Davidson R, Schwartz G, Shapiro D eds. Plenum Press New York. 1986; 4: 1-18.
251. van Norren D, van der Kraats J. Retinal densitometer with the size of a fundus camera. Vis Res 1989; 29: 369-374.
252. van Norren D, van der Kraats J. User friendly system for electrodiagnosis. Doc Ophthalmol 1984; 58: 251-256.
253. Novelli G, Gennarelli M, Menagazzo E. (CTG)n triplet mutation and phenotype manifestations in mnyotonic dystrophy patients. Biochem Med Metab Biol 1993; 50 ; 85/92.
254. Nowak T, Ionescu V, Anuras S. Gastrointestinal manifestations of the muscular dystrophies. Gastro- enterology 1982; 82: 800-810.
255. O'Brien T and Harper P. Course prognosis and complications of childhood onset myotonic dystrophy. Dev Med Child Neurol 1984; 26: 62-67.
256. Ono S, Kurisaki H, Inouye K, Mannen T. 'Ragged -red' fibres in myotonic dystrophy. J Neurol Sci 1986; 74: 247-255.
257. Ono S, Inoue K, Mannen T, Kanda F, Jinnai K, Takahashi K. Neuropathological findings of the brain in myotonic dystrophy- some new observations. J Neurol Sci 1987; 81: 301-320.
258. Oohira A, Goto K, Ozawa T. Slow saccades in myogenic and peripheral neurogenic ophthalmoplegia: latent ocular myopathy in myotonic dystrophy. Neuro-Ophthalmol 1985; 5: 117-124.
259. Op de Coul A, Kortbeek L, Een patient met dystrophia myotonica, longcarcinoom en electroencephalografische afwijkingen. Ned T Geneesk 1967; 111: 26: 1159-1163.
260. Optican L, Chu F, Hays A, Reingold D, Zee D. Adaptive changes of oculomotor performance in abducens nerve palsy. Soc Neurosci (abstr) 1982; 8: 418.
261. Portnoy R and Aronson A. Diadochokinetic syllable rate and regularity in normal and in spastic and ataxic dysarthric subjects. J Speech Hear Dis 1982: 47: 324-328.
262. Panayiopoulos C, Scarpalezos S. Dystrophia myotonica: a model of combined neural and myopathic muscular atrophy. J Neurol Sci 1977; 31: 261-268.
263. Peachy L. The structure of the extra-ocular muscle fibers of mammals. In: The Control of Eye Movements. Bach-y-Rita CC. Collins C and Hyde J eds. Academic Press New York 1971: 47-66.
264. Pena C. Intracytoplasmatic neuronal inclusions in the human thalamus. Lightmicrosopic, histochemical and ultrastructural observations. Acta Neuropathol 1980; 52: 157-159.
265. Pendefunda G, Cernea P, Dobrescu G. Manifestarile oculare in miotonia atrofica Steinert. Oftalmol Zh 1964; 8: 219-224.
266. Penrose L. The problem of anticipation in pedigrees of dystrophia myotonica. Ann Eugen London 1948; 14: 125-232.
267. Perini G, Colombo G, Armani M, Pelligrini A, Ermani M, Miotti M, Angelli C. Intellectual impairmaent and cognitive evoked potentials in myotonic dystrophy. J Nerv Ment Dis 1989; 17: 750-754.
268. Perret E, Eggenberger E, Siegfried J. Simple and complex finger movement performance of patients with Parkinsonism before and after a unilateral stereotactic thalamotomy. J Neurol Neurosurg Psychiatry 1970; 33: 16-21.
269. Pettengell K, Spitaels J, Simjee A. Dysphagia and dystrophia myotonica- a case report. S Afr Med 1985; 68: 113-114.

270. Pinto F, Amantini A, de Scisciolo G, Scaioli V, Frosini R, Pizzi A, Marconi G. Electrophysiological studies of the visual system in myotonic dystrophy. Acta Neur Scand 1987; 76: 351-358.
271. de Pipo K, Holas M, Reding M. Validation of the 3-oz swallow test for aspiration following stroke. Arch Neurol 1992; 49: 1259- 1261.
272. Pizzuti A, Friedman D, Caskey T. The myotonic dystrophy gene. Arch Neurol 1993; 50: 1173-1179.
273. Pokorny J, Smith V, Verriest G, and Pinckers A. Congenital and acquired color vision defects. New York, Grune and Stratton eds. 1979: 106-122.
274. Polgar J, Bradley W, Upton A, Anderson J, Howat J, Pepito F, Roberts D, Scopa J. The early detection of dystrophia myotonica. Brain 1972; 95: 761-776.
275. Portwood M, Wicks J, Lieberman J, Duveneck M. Intellectual and cognitive function in adults with myotonic muscular dystrophy. Arch Phys Med Rehabil 1986; 67: 299-303.
276. Portnoy R, Aronson A. Diadochokinetic syllable rate and regularity in normal and in spastic and in ataxic dysarthric subjects. J Speech Hear Dis 1982: 47: 324-328.
277. Pryse-Phillips W, Johnson G, Larsen B. Incomplete manifestations of myotonic dystrophy in a large kinship in Labrador. Ann Neurol 1982; 11: 582-591.
278. Prudzanski W and Huvos A. Smooth muscle involvement in primary muscle disease. Arch Pathol 1967; 83: 229-233.
279. Ptacek L, Johnson K, Griggs R. Genetics and physiology of the myotonic muscle disorders. New Engl J Med. 1993; 7: 482-489.
280. Ragazzoni A, Pinto F, Taiuti R, Silveri M. Myotonic dystrophy: an electrophysiological study of cognitive deficits. Can J Neurol Sci 1991; 18: 300-306.
281. Ramig L, Scherer R, Titze I, Ringel S. Acoustic analysis of voices of patients with neurologic disease: rationale and preliminary data. Ann Otorhinolaryngol 1988: 97: 164-172.
282. Ravin A, Waring J. Studies in dystrophia myotonica.1. Hereditary aspects Am J Med Sci 1939; 197: 593- 609.
283. Reardon J, Harley H, Brook J, Rundle S, Crow S, Harper P, Shaw D. Minimal expression of myotonic dystrophy: a clinical and molecular analysis. J Med Genet 1992; 29: 770-773.
284. Reetz H. A fast expert program for pitch extraction. In: Proceedings of Euro-speech 1989; 1: 476-479.
285. Reitan R. Validity of the Trail Making Test as an indicator of organic brain damage. Percept Mot Skills, 1958; 8: 271-276.
286. Refsum S. Luft encephalographie in dystrophia myotonica. Nord Med 1961; 65: 822-824.
287. Refsum S, Lonnum A, Sjaastad D, Engeset A. Dystrophia myotonica: repeated pneumoencephalographic studies in ten patients. Neurology 1967; 17: 345-348.
288. Renaud J, Desnuelle C, Schmid-Antromarchi H, Hughes M, Serratrice G, Lazdunski M. Expression of apamin receptor in muscle of patients with myotonic dystrophy. Nature 1986; 319: 678-680.
289. Rezai K, Andrerasen N, Alliger A, Cohen G, Swayze V, O'Leary D. The neuropsychology of the prefrontal cortex. Arch Neurol 1993; 50: 636-642.
290. Ringel S, Wilson W, Barden M, Kaiser K. Histochemistry of human extra-ocular muscle. Arch Ophthalmol 1978; 96: 1067-1072.
291. Robinson D. Oculomotor control signals. In. Basic Mechanisms of Ocular Motility and Their Clinical Implications, Lennerstrand G, Bach-y-Rita P eds. Oxford, Pergamon Press, 1975: 337-374.
292. Robinson D, Sutton G. Age effect in Hearing - A comparative analysis of published threshold data. Audiology 1979; 18: 320-334.
293. Robinson T, James M, Lange K, Owen A, Quinn N, Marsden C. Cognitive performance in multiple system atrophy. Brain 1992; 115. 271-291.
294. Roses A, Apple S. Protein kinase activity in erythrocytes ghosts of patients with myotonic muscular dystrophy. Proc Natl Acad Sci USA 1973; 70: 1855-1859.

295 Roses A, Apple S Muscle membrane protein kinase in myotonic muscular dystrophy Nature 1974, 250 245-247

296 Roses A Myotonic dystrophy Trends Genet 1992, 8

297 Roses A Molecular genetics of neurodegenerative diseases Curr Med Res Opin Neurol 1993, 6 34-39

298 Rosman N, Kakulas B Mental deficiency associated with muscular dystrophy Brain, 1966 89 769- 787

299 Rouques L La myotonie atrophique (maladie de Steinert) Thesis Paris 1931

300 Roy F 'Ocular differential diagnosis' 4th edition Lea and Febiger eds Philadelphia-London 1989

301 Ruedel R, Ruppersberg J, Spittelmeister W Abnormalities of the fast sodium current in myotonic dystrophy, recessive generalized myotonia, and adynamica episodica Muscle Nerve 1989, 12 281-287

302 Sandrini G, Gelmi C, Rossi V, Bianchi P, Alfonsi E, Pachetti C, Verri A, Nappi G Electroretinographic and visual evoked potential abnormalities in myotonic dystrophy Electroenceph Clin Neurophysiol 1986, 65 215-217

303 Sarai K, Ishino H, Yoshioka T, Ogura K, Gomyoda M An autopsy case of myotonia dystrophia Clin Neurol (Tokyo) 1969, 9 1-7

304 Sarks J, Liu H, Killingsworth H, Horowitz G, Penfold P, Sarks S Aust NZ J Ophthalmol 1985, 13 19-36

305 SAS User's Guide Statistics, version 5th edition Cary NC SAS Institute Inc 1985

306 Shallice T From neuropsychology to mental structure Cambridge Cambridge University Press 1988 328- 352

307 Schmid-Antomarchi H, Renaud JF, Romey G The all-or-none role of innervation in expression of apamin receptor and apamin-sensitive Ca++ activated K+ channel in mammalian skeletal muscle Proc Natl Acad Sci USA 1985, 82 2188-2191

308 Schmidt R A schema theory of discrete motor learning Psycholog Rev 1975, 82 225-260

309 Schmidt R The schema as a solution to some persistent problems in motor learning theory In Motor Control Issues and Trends G Stelmach ed New York Academic Press 1976 41-65

310 Schmidt R The schema concept In Human Motor Behavior An Introduction Kelso JAS ed Hillsdale, New Jersey Lawrence Erlbaum Associates 1982 219-235

311 Schmidt R Motor control and learning A behavioral emphasis Champaign, Illinois Human Kinetics Publishers 1988

312 Schalen L Quantification of tracking eye movements in normal subjects Acta Otolaryngol 1980, 90 404- 413

313 Schalen L, Henriksson N, Pykko I Quantification of tracking eye movements in patients with neurolo gical disorders Acta Otolaryngol 1982, 93 387-395

314 Schiller P, True S, Conway J Deficits in eye movements following frontal eye-field and superior colliculus ablations J Neurophysiol 1980, 44 1175-1189

315 Scott A, Collins C Division of labor in human extra-ocular muscle Arch Ophthalmol 1973, 90 319- 322

316 Siciliano G, Rossi L, Fratini F, Falaschi F, Muratorio A Digitalized radiological assessment of pharyngeo-esophageal function in myotonic dystrophy Acta Cardiomiol 1990, 2 45-53

317 Siemerling Fall vom Myotonia congenita, Muskelatrophie und Myasthenia Munch Med Woch 1905, III 1072

318 van Spaendonck K, Berger H, Horstink M, Buytenhuijs E, Cools A Impaired cognitive shifting in Parkinsonian patients on anticholinergic therapy Neuropsychologia 1993 (in press)

319 Spaide R Decreased sympatetic stimulation of the pupils in two patients with myotonic dystrophy Ann Ophthalmol 1984, 16 685-686

320 Stanescu B, Wawernia E Electroretinographic and electroencephalographic changes in dystrophia myotonia Steinert Ophthalmologica 1970, 160 157-166

321. Stanescu B, Michiels J. Temporal aspects of electroretinography in patients with myotonic dystrophy. Am J Ophthalmol 1975; 80: 224-226.
322. Starkstein S, Brandt J, Folstein S, Strauss M, Berthier M, Pearlson G. Neuropsychological and neuroradiological correlates in Huntington's disease. J Neurol Neurosurg Psychiatry 1988; 51: 1259- 1263.
323. Steinert H. Ueber das Klinische und anatomische Bild des Muskelschwundes der Myotoniker (Myopathologi- sche Beitrage) Dtsch Z Nervenheilkd 1909; 37: 58.
324. Stell R, Bronstein A, Plant G, Harding A. Ataxia teleangiectasia: a reappraisal of the ocular motor features and their value in the diagnosis of atypical cases. Movement disorders 1989; 4: 320-329.
325. Stern L, Harold E, Crebo A. Abnormal iris vasculature in myotonic dystrophy. Arch Neurol 1978; 35: 224-227.
326. Streib E, Sun S. Distribution of electrical myotonia in myotonic muscular dystrophy. Neurology 1987; 14: 80-82.
327. Stroop J. Studies of interference in serial verbal reactions. J Exp Psychol 1935; 18: 643-662.
328. Stuss D, Kates M, Poirier C, Hylton D, Hunphreys P, Keene D, Lafleche G. Evaluation of information- processing speed and neuro-psychological functioning in patients with myotonic dystrophy. J Clin Exp Neuropsychol 1987; 9: 131-146.
329. Swick H, Werlin S, Dodds W, Hogan W. Pharyngoesophagal motor function in patients with myotonic dystrophy. Ann Neurol 1981: 10: 454-457.
330. Taylor A, Saint-Cyr J, Lang A. Frontal lobe dysfunction in Parkinson's disease. Brain 1986; 109: 845- 883.
331. Taylor A, Saint-Cyr J, Lang A. Memory and learning in early Parkinson's disease: evidence for a "frontal lobe syndrome". Brain Cognition 1990; 13: 211-232.
332. Theunissen E, Huygen P, Folgering H, Nicolasen M. The velocity step test: its use in the evaluation of the effects of drugs in dizzy patients. Acta Otolaryngol (suppl) 1989; 460: 104-113.
333. Theunissen E, Huygen P, Folgering H. Vestibular hyperreactivity and hyperventilation. Clin Otolaryngol 1986; 11:161-169.
334. Thomasen E. Myotonia: Thomsen's disease (Myotonica congenita), Paramyotonia, and Dystrophia myotonica. A clinical and heredobiologic investigation. Thesis Aarhus Denmark 1948.
335. Thompson D, Woodward J, Ringel S, Nelson L. Evoked potentials in myotonic dystrophy. Electroenceph Clin Neurophysiol 1983; 56: 453-456.
336. Thoonen G, Maassen B. Consonant feature retention patterns in developmental verbal dyspraxia. ASHA Convention Program 1992; 34: 19.
337. Thornton C, Johnson K, Moxley R. Myotonic dystrophy patients have larger CTG expansions in skeletal muscle than leucocytes. Ann Neurol 1994; 35: 104-107.
338. Tsilfidis C, Mackenzie A, Shutler G, Leblond S, Baily J, Johnson K, Wiliiamson R, Siegel-Bartelt J, Korneluk R. D19S51 is closely linked with and maps distal to the myotonic dystrophy locus on 19q. Am J Hum Genet 1991; 49: 961-965.
339. Umeda Y, Sakata E. The circular eye-tracking test. ORL 1975; 37: 290-298.
340. van de Ven P, Janssen G, van Kuppevelt T, Perryman M, Lupa M, Dunne P, ter Laak H, Jap P, Veerkamp J, Epstein H, Wieringa B. Hum Mol Genet 1993; 1889-1894.
341. Verhagen W, ter Bruggen J, Huygen P. Oculomotor, auditory and vestibular responses in myotonic dystrophy. Arch Neurol 1992; 49: 954-960.
342. Vogt A. Die Katarakt bei myotonischer Dystrophie. Graefes Arch Clin Exp Ophthalmol 1922; 108: 212.
343. Vogt A. Die Katarakt bei myotonischer Dystrophie.Lehrbuch und Atlas der Spaltlampenmikroskopie, 1931; 2: 559-565.
344. Vos T. Cataracta myotonica. Thesis Groningen NL 1936.
345. Walker S, Brubaker R, Nagtaki S. Hypotonie and aqueous dynamics in myotonic dystrophy. Invest Ophthalmol Vis Sci 1982; 20: 161-167.

346. Walker G, Rosser R, Matalgia F, Walton J. Psychometric and cranial CT study in myotonic dystrophy. Clin Exp Neurol 1984; 20: 161-167.
347. Warabi T, Kase M, Kato T. Efect of aging on the accuracy of visually guided saccadic movement. Ann Neurol; 16: 449-454.
348. Weber R, Daroff R. Corrective movements following refixation saccades: type and control system analysis. Vis Res 1972; 12: 467-475.
349. Weinberg B, Bosma J, Shanks J, de Meyer W. Myotonic dystrophy initially manifested by speech disability. J Speech Hear Res 1968; 33: 51-55.
350. West J, Numan R, Murphy B, Scheuer T, Catterall W. A phosphorylation site in the Na+ channel required for modulation by protein kinase C. Science 1991; 254: 866-868.
351. Wevers R, Joosten E, Biezenbos J, Theewes A, Veerkamp J. Excessive plasma K+ increase after ischaemic excercise in myotonic muscular dystrophy. Muscle Nerve 1990; 13: 27-32.
352. Whitehead A, Solomon E, Chambers S, Bodmer W, Povey S, Fey G. Assignment of the structural gene for the third component of human complement to chromosome 19. Proc Natl Acad Sci USA 1982; 79: 5021- 5025.
353. Wilson H, Olson W, Gascon G, Brumback R. Personality characteristics and multiple sclerosis. Psych Rep 1982; 1: 791-806.
354. Winer B, Brown D, Michels K. Statistical Principles in Experimental Design. New York: McGraw-Hill, Inc 1991.
355. Wisniewski H, Berry K, Spiro A. Ultrastructure of thalamic neuronal inclusions in myotonic dystrophy. J Neurol Sci 1975; 24: 321-329.
356. Wit J, Maassen B, Gabreels G, Thoonen G. Maximum Performance Tests in children with developmental spastic dysarthria. J Speech Hear Res 1993; 36: 452-460.
357. Wit J, Maasen B, Gabreëls F, Thoonen G. Traumatic versus perinatal spastic dysarthria: assessment by means of speech -like maximum performance tasks. Dev Med Child Neurol (in press).
358. Woodward J, Heaton R, Simon D, Ringel S. Neuropsychological findings in myotonic dystrophy. J Clin Neuropsychol 1982; 4: 335-342.
359. Wright R, Glantz R, Butcher J. Hearing loss in myotonic dystrophy. Ann Neurol 1988; 23: 202-203.
360. Yang J and Barchi R. Phosphorylation of the rat muscle sodiumchannel by cyclic AMP-dependent protein kinase. J Neurochem 1990; 54: 954-962.
361. Yamamoto M, Koga Y, Ohtaki E, Nonaka I. Focal cytochrome c-oxidase deficiency in various neuromuscular diseases. J Neurol Sci 1989; 91; 1: 2: 207-213.
362. Yamane M, Nomura Y. Analysis of stapedial reflex in neuromuscular diseases. J Otolaryngol Relat Spec 1984; 46: 84-96.
363. Ylikoski R, Ylikoski A, Erkinjuntti T, Sulkava R, Rainiinko R, Tilvis R. White matter changes in healthy elderly persons correlate with attention and speed of mental processing. Arch Neurol 1993; 50: 818- 824.
364. Yoshihiro K, Motohiro K, Makoto T, Sadao T. Retinal changes in myotonic dystrophy: clinical and follow-up evaluation. Retina 1993; 13: 129-135.
365. Yoshimura N, Otake M, Igarishi K, Matsunga M, Takebe K, Kudo H. Topography of Alzheimer's neurofibril lary change distribution in myotonic dystrophy. Clin Neuropathol 1990; 9: 234-239.
366. Verwey N, Legras A. Myotonica atrophica, ziekte van Steinert. Ned T Geneesk 1933; 4525-4535.
367. Wieringa B. Commentary: myotonic dystrophy reviewed: back to the future? Human molecular genetics 1994; 3: 1: 1-7.
368. Zakrisson J, Blom S. The relaxation time of the stapedius reflex in dystrophia myotonica (Steinert). Acta Otolaryngol 1982; 94: 473-477.
369. Zauberman H, Magora A. Excitation-inhibition anomalies of the extra-ocular muscles: electromyographic observations. Acta Ophthalmol 1969; 47: 208-214.

370 Zeithofer J, Rasinger G, Mayr N, Mamoli B Changes in brainstem potentials in dystrophia myotonica EEG- EMG 1986, 17 209-212

371 Ziegler W, Hoole P, Hartmann E, von Cramon D Accelerated speech in dysarthria after acquired brain injury acoustic correlates Br J Dis Comm 1988, 23 215-228

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CURRICULUM VITAE

De auteur van dit proefschrift werd op 11 december 1954 geboren te Meppel. Na het behalen van het eindiploma gymnasium beta in 1973 ging hij geneeskunde studeren aan de Universiteit te Groningen. Tijdens zijn studie was hij als student-assistent werkzaam op de afdeling Immunologie. In 1979 en 1980 werden respectievelijk het doctoraal examen, ECFMG en artsexamen behaald.
Zijn opleiding tot neuroloog vond plaats van 1982 tot 1986 in het St. Elisabeth Ziekenhuis te Tilburg (opleider Dr. A.A.W. Op de Coul). De aantekening klinische neurofysiologie werd behaald in het St. Antonius Ziekenhuis te Nieuwegein (opleider Dr. R.G.A Ackerstaff) in 1987. Van 1987 tot 1990 was hij als neuroloog werkzaam in het Academisch Ziekenhuis te Utrecht. Vervolgens werd een chef de clinique functie neurologie respectievelijk neurofysiologie bekleed in het de Wever Ziekenhuis te Heerlen en in het Academisch Ziekenhuis Maastricht. Sinds juli 1992 is hij werkzaam als neuroloog in het Bosch Medicentrum, locatie Willem Alexander Ziekenhuis te 's-Hertogenbosch.

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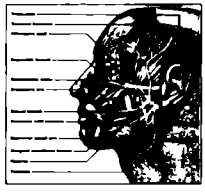

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STELLINGEN

behorende bij het proefschrift

MYOTONIC DYSTROPHY: A QUANTIFICATION OF SOME CLINICAL ASPECTS OF THE CLASSICAL FORM

Jan Pieter ter Bruggen

16 september 1994

I

Ook in het DNA tijdperk is selectief gekozen aanvullende diagnostiek bij MyD geen overbodige luxe (dit proefschrift).

II

De retina is naast de spier een potentieel membraan-model voor K+ homeostasis bij MyD (dit proefschrift).

III

Spraak- en oogbewegings-analyse dient een belangrijker plaats te verkrijgen bij het onderzoek naar vroeg-expressie van het MyD gen (dit proefschrift).

IV

Quantitatieve functionele testen aangaande slikstoornissen en periorale spierzwakte zijn geschikt als parameter voor follow up bij MyD (dit proefschrift).

V

Twee condities zijn nodig om aan iets betekenis te ontlenen: het moet simpel zijn en herhaalbaar (The way of transformation, K.G. Durkheim, 1988)

VI

'Alle medici in dienstverband, zou veel structurele problemen in de gezondheidszorg oplossen', (Het medisch universum, W.F. Hermans, 1954) maar de regelgeving en de lengte der wachtlijsten zullen vermoedelijk eerder toe dan afnemen, zodat de poging van de Commissie Biesheuvel toch als 'schipperen' dient te worden afgedaan.

VII

Bekwaamheid en grootheid dient men niet te meten aan het succes maar aan de deugdzaamheid (Oraculo manual y arte de prudentia, B. Gracian, 1647).

VIII

Het vergaren van kennis is geen aaneenrijgen van nieuwe feiten, maar in het licht der voortdurend veranderende inzichten, een door inspiratie verkregen groeiend besef van eenheid achter de veelheid van actuele hypothesen (vrij naar: Heracleitos, 504 BC).

IX

Hoogwaardige wetenschap bedrijven en succes oogsten biedt geen garantie dat de geldstroom wordt gecontinueerd. Dit pleit voor wetenschapsbeoefening vanuit een pragmatisch nevenberoep (Ethica, Spinoza, 1677).

X

De wetenschap dient als amusement te worden bedreven, maar kan door contingentie en serependiteit tot grootse ontdekkingen leiden (The Origin of Species, C. Darwin, 1859).

XI

Medische expertise blijkt niet zozeer te berusten op superieure redenatie, vaardigheid en pathofysiologische inzichten, maar weet hebben van het 'archetype' van de ziekte en concrete gevallen (A cognitive perspective, Schmidt, 1990).

XII

Drie maal per week lichaamsbeweging bevordert de gezondheid en verlengt de levensverwachting (G. Fletcher, Circulation 1990; 82; 2286–322). Vandaar dat vragen naar lichaamsbeweging in wezen bij elk routine arts-patiënt contact aan de orde zou moeten komen.

XIII

'Veel is mooi en groot is prachtig', maar men moet veel gestudeerd hebben om weinig echt te weten (De 'waarde-ring', Maarten Toonder, 1971).

XIV

Een grotere woon-werk afstand biedt voordelen wat betreft mogelijkheden tot bezinning op wetenschappelijke problemen.

XV

Capaciteit is niet de grootste verworvenheid van de menselijke geest maar flexibiliteit (Ever since Darwin, S.J. Gould, 1977). Het zal dus ongetwijfeld lang duren eer kunstmatige intelligentie het domein van het brein verovert.

XVI

Het moet ons Nederlanders met een grote nautische historie toch als muziek in de oren klinken, dat enorme galjoenen het telkens weer afleggen tegen de kleine, wendbare en slagvaardige vaartuigen. Waarom dan te streven naar steeds grotere fusie-ziekenhuizen? Een bilocatie model zou dan toch te prefereren zijn boven een moloch van een ziekenhuis.

XVII

De ontrafeling van de mysterieuze relatie tussen genotype en fenotype van de ziekte myotone dystrophie is nog immer een 'brug te ver'.