Clinical Documentation for QbTest in Patients With ADHD

1. Background

QbTest is an objective test that is used during neuropsychiatric assessment and for the evaluation of different treatments in patients with ADHD. The test combines a continuous performance test (CPT) with a simultaneous high resolution motion tracking system providing data on all core signs of ADHD, that is, hyperactivity, impulsivity and inattention. The test can be used in children (6-12 years) and in adolescents and adults (12-60 years). The CPT differs in cognitive demand between the child version (Go/No-Go paradigm) and the adolescent/adult version (unconditional identical pair paradigm). The present document describes the principal clinical documentation supporting the use of QbTest in the assessment of ADHD and for treatment follow-up in patients with ADHD. Some of the referred studies below have been performed by Qbtech to evaluate the most fundamental features of the test. These studies are referred to as Data on file and can be delivered at request. However, most of the studies have been performed by different independent research groups and published in peer-reviewed scientific journals.

2. Normative Data

To evaluate a given test person's QbTest performance, a representative control group is needed as comparison. Therefore, normative tests have been gathered from several different cohorts resulting in a normative database of 1307 individuals between 6 and 60 years with an even age and gender distribution. The characteristics of this norm database and the methods to generate age and gender specific comparisons are described in study 1. The age dependent development of QbTest performance in children is described in study 2.

3. Validity Studies

The test is not designed to be a stand-alone tool for the diagnosis of ADHD, rather it should be used as a complement to a structured clinical interview including subjective information by use of validated rating scales. It is, however, important that QbTest can differentiate patients with ADHD from normative individuals. To evaluate this capability, two discriminant validity studies (3-4) were performed, one in children with ADHD (n= 86) and one in adolescents/adults with ADHD (n=135). In both studies, age matched normative individuals were used as control group. Both test versions showed sensitivity (correct classification of individuals with ADHD) and specificity (correct classification of non-clinical individuals) of around 90% supporting that the test can be a valuable tool in the assessment of ADHD. A study (5) in 266 individuals (148 males), with a mean age of 22 years old (13-53 years) was performed to evaluate if computer experience was associated with QbTest performance for the adolescent/adult version of the test. Pearson correlations were conducted examining relations between weekly time spent with computers and/or video-console games and QbTest performance. No correlations were observed, indicating that computer experience is unlikely to be a confounder for the adolescent/adult version of QbTest and does not seem to increase the risk of false negative results.

In addition, 14 published studies (6-18) have evaluated the clinical validity of QbTest. In study 6, fifty clinical cases (5-15 years old) subjected to assessment for ADHD were used to evaluate the ability of QbTest to identify ADHD in a clinical population. The study showed a 96% sensitivity and an 81% specificity of the test to differentiate individuals with ADHD from individuals with disconfirmed ADHD.

Study 7 examined the discriminant validity of the test in a sample of 55 adult patients with ADHD (mean age 33 years) and 202 normative participants (mean age 31 years). A composite measure of ADHD based on three cardinal symptom variables from the test representing hyperactivity, inattention, and impulsivity yielded 86% sensitivity and 83% specificity.

In study 8, with the primary objective to evaluate if the hyperactivity measured during the test not only is present in children but also in adults with ADHD, 20 adult patients diagnosed with ADHD (mean age 37.3 years) and 20 matched healthy controls (mean age 37.5 years) were included and QbTest results compared. The study showed that not only inattention but also hyperactivity, measured by QbTest, was statistically significantly more prominent in ADHD than in controls, increased with the duration of testing, and only covaried with cognitive performance in the subjects with ADHD.

In study 9, with the primary objective to correlate biochemical brain markers with objective measurements for ADHD, 21 children with ADHD (mean age 8.9) and 21 normative children (mean age 11.0) were included. Group comparisons on QbTest performance revealed statistically significant differences between the ADHD and normative group. In addition, several QbTest variables were associated with different biochemical brain markers in the ADHD group.

In study 10 it was shown, both for children and adolescents, that QbTest increased the diagnostic accuracy ($p<0,01$) when used during clinical assessment of ADHD as measured by subsequent rates of revised diagnosis over a 12-month period. The study included 46 subjects (mean age 9 years) in the control group and 62 subjects (mean age 10.5) in the QbTest group. In a similar way, the researchers in study 11 could show that the number of visits needed to diagnose ADHD could be statistically significantly reduced ($p< 0,02$) when QbTest was added to the process. In this study 80 children were evaluated, 40 in the control group (mean age 8.1 years) and 40 in the QbTest group (mean age 9.2 years).

In study 12, an exploratory factor-analysis was performed in 828 children, resulting in a three-factor model representing Hyperactivity, Inattention and Impulsivity respectively. Hyperactivity explained the largest amount of variance and the two other factors, Inattention and Impulsivity, each explained additional unique parts of variance. Convergent validity with the Conner's teacher rating scales was observed for the Hyperactivity factor but not for the Inattention and Impulsivity factors. It was hypothesized that teachers are better able to detect externalizing behavior (i.e., hyperactivity) that is highly visible in classroom situations than internalizing behavior (i.e., inattention), that normally does not disturb classroom proceedings. Also, the relatively low correlations between the subjective and objective methods was explained by the fact that these two methods measure different aspects of behavior.

In study 13, the factors above (Hyperactivity, Inattention and Impulsivity) were evaluated in 45 ADHD children (mean age 9.2 years), 22 non-affected siblings (mean age 11.2 years), and 45 unrelated controls (mean age 8.9 years) with no family history of ADHD. The ADHD children showed the greatest impairments on all three QbTest factors, followed by their non-affected siblings, with control children showing the lowest scores. Group differences between the non-affected siblings and controls were only statistically significant for the motion tracking-based Hyperactivity factor indicating that Hyperactivity assessed by QbTest may be a useful intermediate phenotype in ADHD. The authors concluded that since the QbTest factors are based on the neuropsychological level of the disorder they may represent a marker for ADHD that could ultimately help to improve phenotype definition.

Study 14 and 15 evaluated the discriminant validity for the adult version of the test in different psychiatric populations. In one of the studies (14), a naturalistic sample of 61 clinic-referred patients with suspected ADHD, of which 41 patients met the criteria for ADHD and only 20 did not, were used to evaluate the discriminant validity of the three QbTest factors (Hyperactivity, Impulsivity and Inattention).The Impulsivity and Inattention factors showed high stand-alone specificity (80 and 100% respectively) but low stand-alone sensitivity (59 and 36% respectively) whilst the Hyperactivity factor showed moderate stand-alone sensitivity and specificity (68 and 65% respectively). Interestingly, the self-rating scales (ASRS and CSS) showed the inversed results with high sensitivity (90 and 85% respectively) and low specificity (35 and 40% respectively). A stepwise discriminant function analysis showed that a combination of the Hyperactivity and Inattention factors yielded 72.1% correct classification of the individuals with a sensitivity of 87.8% and a specificity of 40.0%. The low specificity could be explained by the fact that the patients were referred by psychiatric clinics to a specialized ADHD clinic due to suspected ADHD and therefore several of the patients that did not meet the diagnostic criteria (control group) had ADHD-like symptoms. In a somewhat larger study (15), a weighted symptom score was developed by operationalizing the three cardinal symptom variables from QbTest representing Hyperactivity, Inattention and Impulsivity to yield a summary score between 0 and 100, with low scores indicating higher likelihood of ADHD. The respective scores for normative individuals (n=179), patient with disconfirmed ADHD diagnosis (n=29), patients with Bipolar II/Borderline Personality disorder (n=45) and patients with ADHD (n=53) were 71, 40, 46, and 18. The ADHD group scored statistically significantly lower than all other groups and the normative group scored statistically significantly higher than all other groups, indicating that a summary score from the test in an adult population not only can differentiate ADHD from norm but also from other clinical groups.

Another study (16) in an adult clinical population under assessment for ADHD (n=108) evaluated which variables commonly used in different objective tests during neuropsychiatric assessments best predicted final clinical diagnosis. The study showed that the variables with best validity were the cardinal variables for hyperactivity (QbActivity) and inattention (QbInattention) from QbTest, and the variable Commission Errors used in Conner's CPT II. When these variables were used in combination with DIVA (Diagnostic Interview for ADHD in adults), the specificity of the diagnosis was increased by 10%.
Two studies (17-18) have evaluated the ability for QbTest to differentiate ADHD from ASD (Autism Spectrum Disorder). One of the studies (17) included 182 children that had been referred to a specialist clinic for the assessment of ADHD/ASD. Of these children, 124 received a clinical diagnosis of ADHD and 58 received other clinical diagnoses (82% ASD). In this study, the Hyperactivity and Inattention cardinal variables (QbActivity and QbInattention) could differentiate these clinical groups with a statistical significance of $p< 0.01$. These cardinal variables were more effective in predicting ADHD (PPV 0.76–0.86) than in ruling out ADHD in children that predominantly had ASD (NPV 0.37–0.50). The authors concluded that the test variables showed high validity in differentiating ADHD from normatives and moderate validity in differentiating other clinical groups. Study 18 examined QbTest's ability to differentiate ADHD from ASD in an adult population. In similarity with the study performed in children, QbActivity ($p <0.001$) and QbInAttention ($p <0.001$) were the most effective variables in differentiating ADHD from ASD, but also the cardinal variable for impulsivity (QbImpulsivity) showed a statistically significant effect in this respect ($p<0.01$). By adding the information from QbTest to the results from the subjective rating scales, the correct classification of the patients could be increased from 84-94% (ADHD) and from 76-84% (ASD).

4. Reliability Studies

To evaluate the reliability of QbTest, two test-retest studies (19, 20) using similar methodology, were performed in children and adolescents/adults. The study in children included 24 individuals (mean age 11 years) and the study in adolescents/adults included 37 individuals (mean age 25 years). Paired sample correlations for the two test occasions revealed adequate to high retest correlations for the majority of the standard QbTest variables.

5. Treatment Response

Several published studies (21-30) in children, adolescents and adults have been performed in which QbTest was used to evaluate treatment response:

In one study (21) with the objective to evaluate the effect of atomoxetine by means of QbTest and clinical rating scales, 128 children with ADHD, aged 6-12 years, were randomized to treatment with atomoxetine or placebo and followed for 8 weeks. A QbTest was performed three times per day at baseline and after 1, 2, 4, 6 and 8 weeks of treatment. The study showed statistically significant effects after 8 weeks of treatment for all QbTest variables. In addition, the observed effects were corroborated by the validated clinical rating scales used in the study. The highest correlations between the clinical rating scales and QbTest results were around 0.6. Another study (22) in the same child cohort showed that by using QbTest, not only treatment effect over time, but also circadian pattern of treatment response across the day could be measured. Data on placebo response showed that most QbTest variables only changed marginally in the placebo group during the study period, underscoring high reliability for the test.

In a group of 36 children with ADHD aged 8-12 years (23), the effect of immediate-release and long-acting methylphenidate formulations was studied. All included children performed a QbTest four times during the same day within 8 hours. Also in this study, circadian fluctuations on treatment response could be detected by using QbTest. In one study (24) with the objective to identify responders to methylphenidate, 44 children and adolescents aged 7-18 years with confirmed hyperkinetic disorders performed a QbTest before and after a test dose of methylphenidate. A robust treatment response was confirmed in 84% of the patients. Seven percent demonstrated a partial response and 9% were determined as non-responders due to deteriorating activity measures together with no improvement in attention and impulse control measures. The authors concluded that objective measures are effective in the early identification of treatment response to stimulant medication. In one study (25) with the objective to investigate clinical gains from including both dextroamphetamine and methylphenidate in stimulant trials, QbTest was performed in 36 medication-naïve children aged 9-14 years diagnosed with ADHD. By using the QbTest results it could be shown that for an individual child, the two stimulants frequently produced qualitatively or quantitatively different responses. Also in this study, the observed effects using QbTest were corroborated by clinical rating scales.

In a study (26) on the effect of treatment with methylphenidate in 23 adult prisoners (mean age 34.4 years) with ADHD and other coexisting disorders, QbTest was performed after 16 and 52 weeks. The study showed statistically significant effects after 16 weeks of treatment for all QbTest variables. Additional improvements were observed in some parameters after 52 weeks of treatment. In accordance with the findings in studies in children, the observed effects using QbTest were corroborated by clinical rating scales. A study (27) in 63 adult patients (mean age 35.2 years) with ADHD showed that a single dose of methylphenidate (mean dose 13.7 mg) yielded statistically significant ($p<0.001$) decreased symptom levels measured by QbTest for all cardinal symptoms and a weighted symptom score. In a follow-up from the same study, 10 patients were subjected to dose titration of methylphenidate up to 72 mg. The weighted symptom score derived from QbTest, but not the different rating scales used in the study, could identify symptom level reduction between baseline and all investigated dose levels.

Another study (28) compared the treatment response during stimulant treatment in patients with ADHD when measured by use of QbTest or a subjective ADHD rating scale (ADHD-RS). The study showed statistically significant ($p<0.01$) but low correlations (0.33) in Total score changes for the two methods. The QbTest Total score was calculated as the mean value of the three cardinal parameters; QbActivity, QbImpulsivity and QbInattention. The authors suggested that subjectively and objectively measured symptoms may be different ADHD-related constructs. QbTest was more sensitive to medication effects and could objectify an improvement in 54% of patients who did not subjectively report an improvement. Vice versa, 36% of patients not showing objective improvement on the QbTest did subjectively report an improvement. In about half of the cases, the subjective and objective measures agreed in the classification of the treatment effects. High baseline QbTest scores could predict large treatment effects measured both with objective (QbTest) and subjective (ADHD-RS) methods. In contrast, high ADHD-RS scores at base-line were not able to predict treatment effects.

In addition to the studies above on stimulant medication and atomoxetine, QbTest has also been utilized to evaluate the effect of other type of treatments such as essential fatty acid supplementation (29) and cognitive behavior therapy (30).

6. Conclusions

Taken together, the enclosed documentation shows that QbTest is based on a representative control group, show high validity when used to discriminate ADHD from normative individuals and high test-retest reliability. In addition, QbTest can add significant value in the process of differentiating ADHD from similar disorders, improve the diagnostic accuracy, and shorten the time to diagnosis. The effectiveness of the test during treatment follow-up has been documented in different patient populations and for different types of treatments. Several studies showed that the QbTest results were in line with the results from validated rating scales but also added unique information, supporting the usefulness of the test during treatment follow-up. Given the objective nature of the test it should be an important complement to subjective symptom rating scales and clinical interviews.

7. Ongoing Research

In addition to the published studies, numerous additional studies are ongoing in Europe and the US with the objective to further develop and validate QbTest. We collaborate with several research groups specializing in ADHD both in children and adults. The scope of these studies includes: methods to better discriminate ADHD from conditions with similar symptom profiles, prediction of treatment effects, long-term effects of pharmacological treatments, evaluation of non-pharmacological interventions, and clinical utility of QbTest.

8. References

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