APARITO'S GLOBAL IMPACT ON NEURONOPATHIC GAUCHER DISEASE

WHITE PAPER

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OVERCOMING THE DRUG DEVELOPMENT IMPASSE FOR NEURONOPATHIC GAUCHER DISEASE

Gaucher disease (GD) is one of the most prominent types of sphingolipidoses, which are commonly categorised as lysosomal storage diseases (LSDs). The onset of GD is catalysed by defective GBA1 genes which are responsible for the production of the enzyme Beta-glucocerebrosidase. The incidence of the disease has been projected to occur between 1/40,000 - 1/60,000 births. (1) Common symptoms which have been observed in GD patients include: anaemia, hepatosplenomegaly, fatigue, fracturing of the bone and pain, and irregular bleeding and bruising. GD is identified by type, of which there are several. For instance, type 1 GD is identified by there being no pathophysiological functioning upon the central nervous system — its pathological effect is concentrated on the bone, liver and spleen. However, types 2 and 3 GD, which are described as being neuronopathic (nGD) have an effect on the central nervous system. Treatments for patients of GD include the commonly administered enzyme replacement therapy (ERT) which functions to treat patients with type 1 GD and the non-neurological effects observed in type 3 nGD — and substrate reduction therapy for the treatment of type 1 GD. Currently, no efficacious treatments exist for patients with type 2 nGD.

Aparito's wearable technology, paired with a mobile application can facilitate the drug development process for nGD patients, through providing insights not acknowledged by current conventionally-styled clinical trials. Aparito's technology has the capability to collate real-time data, which pertains to the patient's physical and general wellbeing, allowing for remote analysis by the clinician. The strength of proof of concept for Aparito's technology has been shown in a study where patients with types 1 and 3 GD were assessed.

MEETING THE REQUIREMENTS OF PATIENTS

The ambiguity of what biological indicators comprise a definitive diagnosis for type 2 or 3 nGD, make it incredibly difficult to define patient inclusion criteria for clinical trials. This and the vast disease heterogeneity are some of the reasons why there is a lack of therapeutic treatments for nGD patients, and why the development of new treatments is impeded.

The European Medical Agency (EMA) in 2017 acknowledged the dilemmas faced by patients suffering from GD. (2) The intravenous route of administration for ERT for instance has been noted as being inconvenient for patients. Furthermore, the lack of efficacious drugs for neurological involvement was highlighted, as was the nature through which patients are currently assessed. Clinical environments by nature tend to focus on the pathological particulars, which often yields a neglect of non-physical factors such as mental health and general wellbeing. As highlighted by EMA documentation and the experiences of patients, the need for change in nGD assessment is paramount.

A recent definition of nGD published by experts in the field will support better distinction between types of nGD in imminent clinical trials, and a remote digitised endpoint offers one more viable tool for the challenges faced. (3)

DATA WHICH PROVIDES INSIGHT

The GD study initiated by the UK Gaucher Association in partnership with Aparito recruited a total of 21 patients; recruiting five patients with type 1 GD (with a mean age of 24.8 years), and 16 patients with type 3 nGD (with a mean age of 21 years). The type 3 nGD cohort represented 57% of identified nGD cases in the UK. The study explored the differences in ambulation ability between patients of GD and nGD (type 3) using the commonly deployed Six Minute Walking Test (6MWT), as well as monitoring the average daily steps (ADS) taken, the maximum number of steps taken in a 30 minute period (ADM), and the average number of steps per 30 minute period. The metrics were captured with a 3D accelerometer that was paired with a mobile application downloaded to the patients' mobile device.

- *The 6MWT showed a considerable difference in the distance walked between GD and nGD patients.*
- *The 6MWT mean for nGD patients was 391m (with a z score of -5.57) and 475.67m (with a z score of -3.99) for GD patients.*
- *The relative difference in ambulation was further corroborated by the data obtained from the ADS and ADM metrics.*
- *The ADS for GD patients was almost 2.5 times higher than that of nGD patients (though this comparison was not statistically significant when analysed with the t-test and Mann-Whitney-U Test).*
- *The ADM for GD patients was 1537.25, compared to 554.29 for nGD patients. Analysis with the Pearson Correlation Coefficient showed a correlation between ADM, ADS, and ADE metrics when compared individually with age (r= -0.592, -0.593 and -0.573 respectively); the data showed an inverse relationship between an increase in age and a decrease in physical activity.*
- *Analysis with Kendall's τ Coefficient showed a correlation between the acuteness of bone disease and ADS (Kendall's τ = -0.538)*
- *Analysis with Kendall's τ Coefficient also showed a correlation between kyphosis and ADS (Kendall's τ = -0.367); this finding however was not statistically significant.*

	nGD (TYPE 3)	GD1
Mean age / range (years)	21 (5–48)	24.8 (13–42)
Gender	2 males / 14 females	4 males / 1 female
Six Minute Walking Test (mean) (n=15)	391m (n=12)	475.67 (n=3)
Six Minute Walking Test Z score	-5.57	-3.99
Average Daily Maximum (ADM)	554.29	1537.25
Average Daily Steps (ADS)	3933.64	9805.52
Average Steps per Epoch (ADE)	260.26	489.711

Table 1. Summary of ambulation metrics obtained by the wearable device.

A NEW PATIENT-CENTRIC APPROACH

The mobile application allowed patients to report their experiences in real time; this feature allowed patients to record their symptoms ("events") as they occurred. Nine patients with nGD and two with type 1 GD reported the events they experienced.

- *"Bone pain" appeared to be a major concern for nGD patients, as it formed the largest proportion of recorded events with 48%.*
- *77.8% of nGD patients that recorded the events they experienced acknowledged the presence of "bone pain".*
- *Difficulties experienced with sleep (listed as "sleep") also comprised one of the largest proportions of recorded events with 26%.*
- *6% of recorded events were listed as "other".*

In addition the psychosocial wellbeing of the patients was assessed with use of various qualitative outcome measures which were integrated into the mobile application. The implementation of the paediatric quality of life outcome measure (CHU9D) contrasted the day to day experiences of type 1 GD and nGD patients. The data obtained was depicted as mean scores for each domain with 95% confidence intervals. Tiredness was shown to be a major feature of the nGD patient experience, whereas the debilitating effect on "daily routine" was not as prominent, which was also in alignment with findings where the Mental Fatigue Scale (MFS) and sleep-specific patient reported outcomes were utilised. In the REM Sleep Behaviour Disorder Questionnaire (RSBDQ) issues with sleep were identified in patients with nGD but not in patients with type 1 GD.

Issues with sleep were also identified with use of the Pittsburgh Sleep Quality Index, however the results were not statistically significant. Data obtained from the mobile application that pertained to "sleep disturbances" was also analysed alongside the responses to questionnaires which assessed the quality of sleep. A correlation was identified in this instance, further highlighting the necessity of mitigating the issues related to sleep.

In depth longitudinal data analysis was produced for one nGD patient that engaged with the mobile application and wearable device frequently. The number of steps taken daily for the patient was tracked over a period of 1.5 months. In addition, the patients' responses to the CHU9D outcome measure spanned 10 months (17/10/16 - 17/08/17), and 11 months (01/10/16 - 01/09/17) for the Perceived Stress Scale (PSS).

Overall, when contrasting the CHU9D domain scores of type 1 GD and nGD patients, a statistically significant difference between the cohorts was found. The differences in mean scores were indicative of nGD having a more debilitating effect on patients, relative to the patients with type 1 GD. This could be said to be further corroborated by the findings in the assessment of patients with the PSS metric, in which nGD patients were shown as being considerably more stressed. However, only two patients with type 1 GD produced data for the PSS at the beginning of the study.

The findings highlight the experiences of individuals with GD and nGD, and will provide clinicians and carers with the necessary information to help their patients manage their lifestyles.

TECHNOLOGY THAT CAN DELIVER FOR PATIENTS AND FAMILIES

The study spearheaded by Aparito shows that a digitised approach to the treatment of nGD is a viable alternative to more conventional clinically based methods. The ability to track patients over a prolonged period is pivotal, as the experiences of patients may differ between clinical and more homely environments.

Aparito's technology provides clinicians and those within the drug development sphere with the tools to not only assess patients in person, but also to monitor them remotely. Frequent, undisrupted assembling of data over a prolonged period will provide a rich data set which will highlight the needs of each patient. Furthermore, the technology successfully achieves a personalised approach through the integrating of outcome measures related to the patients' emotional wellbeing; such factors are often overlooked in conventional clinical environments.

Certain challenges are apparent when deploying technological approaches in healthcare. For instance, the study highlighted discrepancies in wearable device/mobile application usage. For some, use of modern technology may be too complex and difficult to navigate around. Such dilemmas however can be curtailed through device and software amendments, which can provide an application interface that patients can interact with more easily.

Therapeutic options for patients with nGD are lacking and the drug development process is hindered due to the nature of the disease. Aparito's technology aims to provide the relevant stakeholders with the rich data sources that they need to address the disease. This can be further delivered as part of a global disease registry soon to be launched by the International Gaucher Alliance, which is also supported by Aparito. (4) The registry approach will be recruiting patients remotely, and such data capture will be greatly facilitated with remote wearable and mobile health tools. This work also has the focus of developing a disease specific Patient Reported Outcome for inclusion in the registry.

With many clinical trials now on the horizon for nGD, the development of previously mentioned tools, definitions, and a disease registry, will all contribute towards helping address the current unmet needs for nGD patients and their families. The study spearheaded by Aparito shows that a digitised approach to the treatment of nGD is a viable alternative to more conventional clinically based methods.

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