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Medical Advances in Diagnosing Neurological and Genetic Disorders

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***Abstract*—**Retinoblastoma is a rare type of childhood genetic cancer that affects children worldwide. The diagnosis is often missed due to lack of education and difficulty in presentation of the tumor. Frequently, the tumor on the retina is noticed by photography when the red-eye flash, commonly seen in normal eyes, is not produced. Instead, a yellow or white colored patch is seen or the child has a noticeable strabismus. Early detection can be life-saving though often results in removal of the affected eye. Remaining functioning in the healthy eye when the child is young has resulted in super-vision and high or above-average intelligence. Technological advancement of cameras has helped in early detection. Brain imaging has also made possible early detection of neurological diseases and, together with the monitoring of cortisol levels and yawning frequency, promises to be the next new early diagnostic tool for the detection of neurological diseases where cortisol insufficiency is particularly salient, such as multiple sclerosis and Cushing's disease.

***Keywords*—**Cortisol, Neurological Disease, Retinoblastoma, Thompson Cortisol Hypothesis, Yawning.

I. Introduction

RETINOBLASTOMA (Rb) is a rare type of eye cancer yet it is the most common intraocular malignancy of early childhood [1]-[3] and continues to form about 3 per cent of all childhood cancers [4]. An aggressive disease, it evolves as a tumor of the retina on the inside at the back of the eye [5].

Although almost exclusively a cancer of childhood, it has been detected in the fetus and can also occur in older children [6]. Rb presents from birth to 5 years of age [7], [8]. In the UK, it affects 40 to 50 children every year [9] and occurs because of errors or mutations to a gene called the RB1 gene [1].

Data for the period of 2006-2010 show a five-year survival rate of 100 per cent, in the UK [9]; however, the survival rate in developed countries averages at 95 per cent compared to 50 per cent worldwide [8] [10]. Delay in presentation, diagnosis and access to resources are the most common explanations for this difference [11].

When both copies of the RB1 gene are damaged in a single cell, followed by a chance mutation in the child's retinal cells, then one of the important "stops" of cell growth and cell division is lost giving rise to tumors in the retina [12]. The RB1 gene is located on chromosome 13, position 14.2 and is a tumor suppressor gene [3]. If the mutated gene is present in the parent with the disease or if the parent is a carrier of the disease, and if the child's retina mutates, then tumors typically occur bilaterally [13] and with a high risk to the brothers and sisters and future children also having the bilateral disease. There are treatment options in these cases but often the child loses substantial sight in one or both eyes and if the tumor is aggressive and large then the eye is also lost and requires surgical implant.

If the RB1 gene does not mutate within the parent but instead mutates in either the egg or sperm, this gives rise to Rb if the child's retinal cells also mutate. Mutation of the RB1 gene may also occur during early embryonic development before the cells are defined, and if mutation occurs in the retina of the unborn child, then Rb can occur unilaterally or bilaterally with lower risk to brothers and sisters and to future children. If the gene mutates in the retina of the healthy child, then Rb often occurs unilaterally with a low risk for brothers and sisters and future children.

The genetic possibilities are "heritable" versus "non-heritable" though "mosaic" has been used when the picture may be less definitive and if some but not all cells carry the mutated gene but only one eye has appeared with Rb tumors.

Early diagnosis is essential if the tumors are to be detected and treated and if the spread of tumor is to be stopped. Often parents may see an unusual color in the eye or eyes of their children when photographed such as a yellow coloring (a little similar to a cod liver oil capsule) or a white color [14] rather than the natural red pigment of the retina [1].

Flash photography using the installed camera of a modern mobile phone (commonly, backside-illuminated 5 megapixel, or greater, rear-facing camera, with 3.85 mm f/2.8 lens) is ideal for detecting the normal "red eye" that should be reflected from the retina [15].

Close-up flash photography in this manner is helpful and often re-assuring as initial screening but parents are advised to seek professional confirmation if there is any doubt about these signs especially since early detection of Rb is of paramount importance.

Loss of a body part not only impacts functionality but it can also affect the individual cosmetically and, in turn, affects the individual's psychological and psychosocial wellbeing. There is a growing trend towards regarding sensory losses as changes to lifestyle that render the person with a new growth and direction for life goals, termed post-traumatic growth [16], rather than sensory deprivation.

Recognizing sensory loss can sometimes result in the person functioning above average with the remaining senses. Being born functionally blind, or losing an eye following trauma (accident or disease, cancer), these children may

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experience heightened aural senses, touch, and olfactory senses [17]. Phantom limb pain has been well documented [18] where patients continue to experience pain and sensations in the amputated limb; and those with prostheses often become accustomed to the loss and to the artificial limb [19].

By compensating for their lack of vision by using their other sensory modalities, blind-sighted individuals often outperform sighted individuals in non-visual tasks such as reading Braille [20] memory retrieval [21] unfamiliar voice recognition [22]; verbal memory [21]; auditory spatial discrimination [23]; and musical abilities [24].

Bowns and colleagues [25] found that early-enucleated adults and controls have a similar threshold for detecting motion. Comparing depth perception, Gonzalez and colleagues [26] found that those with early enucleation had worse depth perception. However, early-enucleated individuals seem to improve visual performance through learning and due to reorganization of cells responsible for sensory modality [27]-[31].

During the first few years of life, cells in the visual system form connections that are strengthened by the amount of sensory information received. These connections form visual functions which can take years to mature [32]. Other researchers [33] found that children enucleated up to four years of age will have neuroplasticity where cell reorganization can occur within hours and involves other sensory modalities [34], [35].

Thompson and Chinnery [15] reported on a case history (PT), diagnosed with retinoblastoma, who underwent unilateral enucleation at 9 months, and has the remaining functional eye with exceptional above-average vision and above-average intelligence. Cases of "super-vision" are not uncommon in those who compensate for sensory loss.

Research into compensation has demonstrated that the loss of one sensory modality can be replaced by another, particularly when the loss occurs at an early age [27]. Neuroplasticity can explain the reasons why functionality can continue despite loss of sensory organs, and that new neural connections are strengthened through experience and practice.

The naturally occurring hormone in humans, cortisol, is considered important for immune protection and stress regulation [36], [37]. Measuring the levels of cortisol is useful for monitoring several medical conditions including cases where high levels of stress are known, adrenal insufficiency, and possibly for certain neurological diseases, such as multiple sclerosis [38].

The connection between cortisol and yawning has only recently been established by the Thompson Cortisol Hypothesis (TCH) [39]. Expansion of the TCH in 2014 [40], has enabled further exploration of the pathways involved during yawning [41] [42], [19], with the proposal that cortisol, in conjunction with the yawning reflex, might provide a potential biomarker for the early detection of neurological disease [43].

Predictors of disease are not new and bio-informatics is increasingly important to our understanding of disease progress and for early detection and treatment and it is now thought that rises in cortisol elicit the yawning response which in turn regulate brain temperature and prevent the brain from over-heating [42], [43]. A series of studies led by the author and his team at Bournemouth University, UK, and in France, have determined that yawning is significantly correlated with cortisol and that the electrical nerve impulses generated from jaw-line muscles, upon yawning, are also correlated with the yawning reflex.

Excessive yawning is proposed as an early indicator of underlying neurological disease, and together with cortisol, may be a potential biomarker in detection techniques.

II. Method and Materials

A. Procedure

Eighty-two volunteers were recruited from students and the research volunteer pool at Bournemouth University using the computerized recruitment system and Facebook. All participants were properly consented according to code of conduct and research guidelines, and exposed, under randomized controlled trials guidelines, to three conditions intended to provoke a yawning response – photos of people yawning; boring text about yawning; short video of person yawning. Comparisons were made with people exposed to the same conditions but who did not yawn.

Saliva samples were collected at start and again after yawning response [Fig. 1], together with electromyography data of the jaw muscles to determine rest and yawning phases of neural activity [Fig. 2].

Fig. 1 Kit to test for cortisol in saliva

If there was no yawning response, then a second saliva sample was taken at the end of the experimental paradigm. Cortisol levels are easily detected in saliva and it is a far less intrusive method than intravenous collection.

Presence of cortisol in saliva is highly correlated with blood assay and it is also cheaper to analyze in the laboratory. A yawning susceptibility scale (questionnaire designed for this study), Hospital Anxiety and Depression Scale (HADS) [44] [45], General Health Questionnaire GHQ28 [46]-[48] and

demographic and health details were also collected from each participant.

Exclusion criteria were: chronic fatigue, diabetes, fibromyalgia, heart condition, high blood pressure, hormone replacement therapy, multiples sclerosis, and stroke. Between- and within-subjects comparisons were made using t-tests and correlations using the SPSS package. This enabled a comparison to be made between yawner and non-yawner participants as well as between rest status and yawning episodes.

Fig. 2 Surface-placed electrodes to portable electromyograph

III. Results

There were no significant differences between groups in terms of age, HADS anxiety and depression scores, and GHQ28 scores. Normative data for saliva cortisol is known, and lies within the following ranges: (a) Morning collection is 3.7 to 9.5 nanograms (one billionth of a gram or 10^{-9}) per milliliter of saliva; (b) Noon collection is 1.2 to 3.0 nanograms per milliliter; (c) Evening collection is 0.6 to 1.9 nanograms per milliliter.

In saliva cortisol sample 1, the means for non-yawners was 2.1 (SD = 1.67), and for yawners was 2.6 (SD = 1.99). In sample 2, the means were 2.2 (SD = 1.72) for non-yawners, and 3.1 (SD = 2.26) for the yawners. Hence, the yawners had higher levels of resting and post-experiment saliva cortisol levels than the non-yawners. In addition, there was a significant difference between sample 1 (saliva cortisol) and sample 2 (saliva cortisol) amongst the yawners: $t(37) = 2.842$, $p = .007$.

For the yawners, at rest, the EMG range was -100 to 200 millionth of a volt (mean of 182.2) as compared with -60 000 to 18 000 (mean of 3 897.4) after yawning. For non-yawners, the range was -80 to 120 (mean of 37.2) and -400 to 800 (mean of 57.5) after the stimuli presentation. Therefore, the yawners tended to show a larger peak following the yawn as compared with the non-yawners, post-stimuli.

IV. Discussion

Significant difference in saliva cortisol levels for those who yawned, between sample one and sample two, were found, which lends support for the Thompson Cortisol Hypothesis. Electromyography activity also increased with elevated cortisol levels and when yawning. This is an exciting finding as cortisol, in conjunction with yawning, may promise to be a potential new diagnostic tool for the early detection of neurological diseases, such as multiple sclerosis.

In an additional paradigm by the author and colleagues, brain scans for each participant who were allocated to mental or motor tasks and who were also tested for saliva cortisol, showed the following brain activity.

For participants with the lowest level of cortisol in the mental condition, there was less activity and less spread of activity in the brain-stem region compared with the corresponding participant in the physical condition. Similar results were shown for these participants on comparing hypothalamus activity, across the whole group of participants [Figs. 3-5].

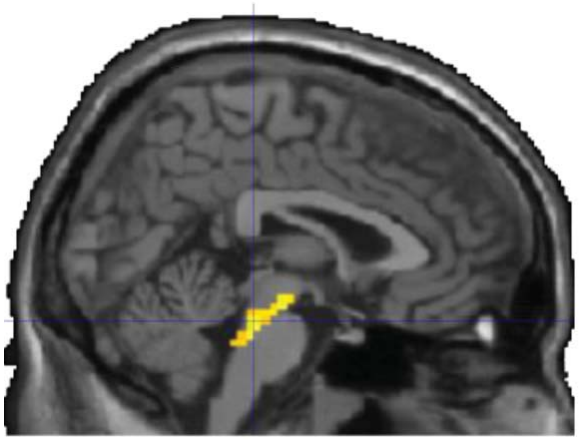

Fig. 3 Brain-stem activity for mental task

Fig. 4 Hypothalamus activity for mental task

In terms of cortical activity, the brain-stem and hypothalamus regions appear to be more active during the

physical condition at low levels of cortisol but the activity is more widespread in the brain-stem region in the mental condition at higher levels of cortisol in participants.

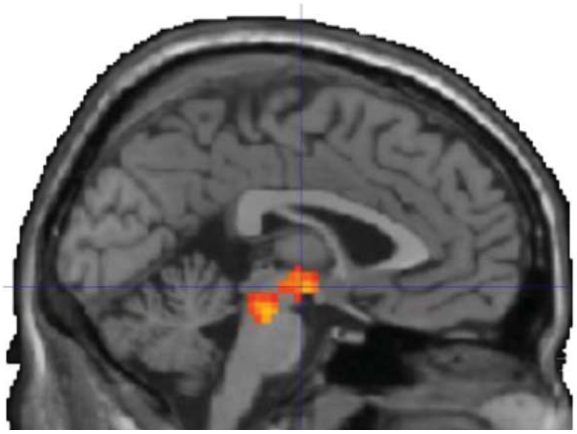

Fig. 5 Brain-stem and hypothalamus activity for physical task

V. Conclusion

Potential application of these findings is in the diagnosis of neurological diseases such as in immune suppression syndromes where cortisol is important for good health maintenance.

The release of cortisol into our circulation system appears to have many roles, including protection and regulation of other neurochemicals. Yawning and cortisol is of particular interest and whilst still presenting a scientific conundrum in terms of its origin and mechanism, research has indicated that it features in a number of neurological disorders as well as in healthy individuals.

Cortisol is of interest to clinical scientists, practitioners, neurologists and neuroscientists because of its importance in stress response within the HPA-axis. Identifying threshold levels of cortisol and the recruitment of brain region activity may be important in determining future functioning deficits and neuronal damage.

Image capturing technology is also particularly useful for the detection for Rb, and with the advent of sophisticated camera technology, early diagnosis of Rb is made more possible. It is hoped that this technology can be put to good use and for the benefit of all individuals who have had neurological or genetic diseases impaired in the near future.

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