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The Epidemiology of Stargardt Disease in the United Kingdom

Kurt Spiteri Cornish, FRCOphth,[1] *Jason Ho, FRCOphth,*[2,3] *Susan Downes, FRCOphth,*[4] *Neil W. Scott, PhD,*[5] *James Bainbridge, PhD,*[2,3] *Noemi Lois, MD, PhD*[6]

Purpose: To establish the incidence of Stargardt disease (STGD) in the United Kingdom and define baseline characteristics of newly diagnosed patients.

Design: Prospective epidemiologic study undertaken under the auspices of the British Ophthalmological Surveillance Unit (BOSU).

Participants: New incident cases of STGD in the United Kingdom reported by ophthalmologists to BOSU during a 12-month period, from June 1, 2012, to June 1, 2013.

Methods: Once a new case of STGD was reported, an incident questionnaire was sent to the reporting ophthalmologist, followed by a follow-up questionnaire (when required) 6 months later.

Main Outcome Measures: Patient demographics, baseline characteristics including visual acuity, and findings on slit-lamp biomicroscopy, as well as diagnostic technologies undertaken at baseline and their findings, including electrophysiology, fundus autofluorescence, fluorescein angiography, and genetic testing.

Results: A total of 81 new cases of STGD were reported during the 12-month period of the study; baseline data were obtained on 70 (86%) of these. These results suggest an annual incidence in the United Kingdom of between 0.110 and 0.128 per 100 000 individuals. The median age of patients at presentation was 27 years, the majority were British (77%), and most (90%) were symptomatic, with a median visual acuity of 0.52 logMAR (Snellen equivalent 20/66).

Conclusions: Even considering possible limitations related to incomplete ascertainment, this is the first prospective epidemiology study that provides indication of the incidence of STGD in the United Kingdom. The incidence of STGD estimated herein appears to be lower than that repeatedly quoted in the literature. Fundus autofluoresence and electrophysiology testing are most commonly used for the evaluation of patients with STGD. *Ophthalmology Retina 2017;■:1–6 © 2017 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Stargardt disease (STGD) and fundus flavimaculatus (FFM) are synonymous terms used to refer to the same recessively inherited macular dystrophy that affects photoreceptor (PR) and retinal pigment epithelium (RPE).[1,2] The condition was first recognized in 1909 by Stargardt, who described 7 patients with a recessively inherited macular dystrophy characterized by macular atrophy surrounded by deep yellow-white retinal lesions.[1] Other features of the disease include initial loss of vision without clinical signs on funduscopy.[1] The term FFM was later coined by Franceschetti, who described a disease characterized by the presence of "fishlike" (pisciform) deep yellow-white retinal lesions, now referred to as "flecks."[2] Since the original description, there have been numerous studies evaluating different aspects of this inherited retinal disorder.

The incidence of STGD was estimated to be between 1 in 8000 and 1 in 10 000 in the United States.[3] The 1 in 10 000 incidence has been repeatedly quoted in the literature.[3–5] This estimate, however, does not derive from an epidemiology study but rather from Blacharski's observation that STGD is more common than retinoblastoma (the incidence of which Blacharski estimated to be 1 in 15 000) but less common than retinitis pigmentosa (which Blacharski estimated to occur in 1 in 5000 individuals). As new therapies for STGD are currently being investigated, including embryonic stem cell–derived retinal pigment epithelial cell transplantation[6] and *ABCA4* gene replacement therapy using the StarGen,[7] elucidating the incidence and baseline characteristics of patients presenting with this macular dystrophy would be invaluable to plan future therapeutic strategies. This was thus the purpose of the study presented herein. In order to accomplish this purpose, we undertook a prospective population-based epidemiologic study to determine the incidence of STGD in the United Kingdom and gain knowledge on the baseline characteristics of patients presenting with this retinal disorder.

Methods

The study was conducted in according with the tenets of the Declaration of Helsinki. Ethical approval was sought and obtained from the North of Scotland National Research Ethics Service and the NHS Grampian Research and Development Committees before the initiation of the study.

Patients with newly diagnosed STGD (new incident cases) were identified prospectively through active surveillance by the British

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Ophthalmological Surveillance Unit (BOSU) during a 12-month period from July 2012 to June 2013, both inclusive. This surveillance scheme involves all ophthalmologists in the United Kingdom (consultants and associate specialists). Before the study was initiated, the BOSU informed ophthalmologists about the new ocular conditions under investigation (STGD), including the case definition. For the purpose of the study, STGD was defined as a recessively inherited retinal dystrophy presenting at any age with a number of characteristics, which include macular changes (mottling, bull's-eye appearance, and/or atrophy) and/or retinal flecks (active or resorbed) with relative peripapillary sparing. An active fleck is defined as an accumulation of yellow material at the level of the RPE, which appears as an area of hypofluorescence on fundus fluorescein angiography (FFA) and as an area of increased signal on autofluorescence (AF) imaging. A resorbed fleck is defined as a small focus of depigmentation or atrophy in the RPE, appearing as an area of hyperfluorescence on FFA and reduced AF signal.

Genetic confirmation (i.e., presence of disease-causing variations in both alleles of the *ABCA4*) was not required for the diagnosis of the cases reported. The diagnosis was made by findings on clinical examination (as per the above description) and ancillary studies including pattern and full-field electroretinography (PERG and FFERG, respectively), fluorescein angiography, and fundus AF. A flat or very reduced PERG (with our without FFERG abnormalities), dark choroid on FFA, and multiple foci or reduced or increased signal on fundus AF imaging with relative peripapillary sparing would be suggestive of the diagnosis. Consultation with national experts on inherited retinal diseases took place before the initiation of the study to set the case definition used.

At the end of each month, a report card was sent out by BOSU to ophthalmologists in the United Kingdom (UK); ophthalmologists then returned the card to BOSU specifying whether a new case had been seen during that month (or whether this had not been the case). After case notification, a study card with the case definition and incident questionnaire was sent to the reporting ophthalmologists by the research group. If the reporting ophthalmologist indicated that further investigations were planned for the patient, a further follow-up questionnaire was sent 6 months after receipt of the incident questionnaire. For this study, units that had not reported cases but that were covering a population sufficiently large to have been expected to have evaluated a case of STGD were independently contacted to confirm the absence of incident STGD cases during the 12-month study period.

Before the initiation of the study, retinal specialists from all over the UK, who were thought to form largely the group that would be most likely reporting new incident cases, were approached and informed about the upcoming study and asked to provide feedback on the study card (case definition) and questionnaires developed for the study. Their input was incorporated in the final materials for the study.

The incident questionnaire collected data on age of onset, gender, ethnicity, family history, and symptoms at presentation. Baseline examination findings including best-corrected visual acuity and fundus features and results of ancillary studies including electrophysiology, AF, FFA, and genetic testing, if available, were also sought. Ophthalmologists were specifically questioned in the incident questionnaire as to whether further testing was planned in the reported case and, if so, follow-up questionnaires were sent at 6 months to collect the results of these tests. To avoid possible reporting duplications related to the fact that patients could be diagnosed in one center and referred to a tertiary center specializing in the diagnosis and evaluation of patients with inherited retinal disorders, nonidentifiable details (date of birth and first part of postcode) were collected from each patient in the incident questionnaire. In the event that a patient was referred to a different hospital, the 2 separate questionnaires would have the same patient details and would be counted as 1 single patient, if this was confirmed to be the case. Reporting ophthalmologists were encouraged to contact KSC or NL in case of doubt about the possible diagnosis of STGD; in some instances, anonymized images and other investigations were, thus, provided to and analyzed by 2 of the authors (KSC and NL) to confirm or exclude the diagnosis of STGD.

Results

New Incident Cases Reported

From July 2012 to June 2013 (both months inclusive), a total of 86 cards were returned to BOSU reporting new incident cases. Of these, 5 cases were excluded: 2 because although they were initially thought to be STGD, they were later diagnosed as cone dystrophy and pattern dystrophy by the reporting ophthalmologist; and 3 because they had been diagnosed outside the specified study period. Thus, there were 81 incident cases; baseline data were obtained through the incident questionnaire in 70 of 81 new incident cases (86%), and follow-up data were obtained in 6 of 7 (85.7%) of the 6-month questionnaires sent. During the study period, there were a total of 1251 reporting ophthalmologists for all BOSU studies and the overall card return rate was 74.5%.

Incidence of Stargardt Disease in the United Kingdom

In 2012, the UK Office for National Statistics projected the population to be 63 700 000. Considering all 81 cases reported to BOSU, the estimated incidence of STGD in the UK would be 0.127 per 100 000 per year (95% confidence interval, 0.099−0.155). If only the 70 cases of STGD for which data were available to the researchers (questionnaires returned) and the diagnosis of STGD confirmed were to be included, then the estimated annual incidence of STGD in the UK would be 0.110 per 100 000 (95% confidence interval, 0.084−0.136) of the general population per year. Therefore these results would suggest an annual incidence of STGD-FFM in the UK of between 0.110 and 0.127 per 100 000 individuals per year.

Patient Demographics

The majority of reported cases of STGD affected young adults, with a median age of 27 years (mean 27.4 years; range 5−64 years). The majority were white British (77%), with a higher proportion of female subjects affected (61.4%). A summary of the baseline characteristics of incident cases is presented in Tables 1 to 3.

Symptoms

The vast majority of cases were symptomatic (90.0%), with reduced vision being the most common symptom (80.0%), followed by nyctalopia (12.9%) and photophobia (11.4%).

Visual Acuity

Visual acuity at presentation was recorded in either Snellen or logarithm of the minimum angle of resolution (logMAR). For the purpose of this study, Snellen visual acuity values were converted into logMAR acuities using standard conversion tables. Visual