LETTERS TO THE EDITOR

Chromosome abnormalities and Williams-Beuren syndrome

Telvi *et al*¹ recently reported on a 27 month old girl with an unbalanced de novo translocation, t(X;21)(q28;q11), and diagnosed this child as having an incomplete form of Williams-Beuren syndrome (WBS). This was based on some symptoms specific to WBS, such as craniofacial dysmorphism, delayed psychomotor development, short stature, horseshoe kidneys, and a positive WBS score of +4.09.² We do not agree with this diagnosis and would like to make some comments.

(1) The facial 'gestalt' is not typical of WBS, especially the upper lips. (2) All patients with blue eyes show a stellate pattern of the iris (personal observation) which is missing in this girl. (3) A colobomatous abnormality in one eye has never been reported in WBS. (4) The girl is still unable to speak. Although developmental delay is frequent in WBS, these children usually start to speak earlier than 27 months. Based on a retrospective study of 122 WBS patients aged between 1½ to 46 years, the mean age of uttering the first words was 20.6 months (SD 9.96). (5) Cardiovascular malformations were not diagnosed in the girl reported by Telvi *et al*¹ but in a total of 125 patients seen by us between 1988 and 1993 cardiovascular features were present in 90% of them, so cardiovascular malformation is a primary symptom of the syndrome. (6) This girl presented with axial hypertonia a symptom we have never seen in WBS children at this age. (7) Some of the frequent symptoms and behaviour seen in young WBS patients are missing in the published girl, such as long neck, hanging shoulders, and narrow trunk. In early infancy, life is very often stressful with feeding difficulties, vomiting, constipation, and sleeping problems. Young patients often show excessive anxiety and hypersensitivity to noise and music.

Besides the seven points mentioned above, the familial case published by Cortada *et al*³ has been questioned and diagnosed later as Noonan syndrome.⁴

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Counselling pitfalls in Romano-Ward syndrome

We wish to comment on several issues raised by the recent paper by Reardon *et al*¹ on counselling pitfalls in Romano-Ward syndrome. We would strongly support their view that pedigree and phenotype analysis in this disorder can prove difficult. The fact that affected subjects may have a normal corrected QT interval (QTc) has been well documented in the past.²

Romano-Ward syndrome is a disorder of ventricular repolarisation, and in the assessment of a patient's status, T and U wave morphology may be helpful,³ as abnormalities are common. Biphasic, bifid, and notched T waves are described,² as are TU fusion waves,^{4,5} and also T wave alternans.⁶ It would be useful to know whether such abnormalities were seen in the family reported by Reardon *et al*,¹ as this might help determine whether a person such as II-1 should be considered affected, despite his normal QTc. The finding that QTc tends to decrease in affected males after the age of 15⁷ may also be relevant.

Another aspect of the assessment of penetrance of the gene for counselling purposes is illustrated by the authors' use of Vincent's data from one family suggesting that only 24% of those at 50% risk of inheriting Romano-Ward had a prolonged QTc. This is not true of every family, however, as in our own study of two families 18/36 and 4/7 persons at 50% risk in each family respectively had prolonged QTc or recognisable T or U wave abnormalities or both. A Japanese study similarly reported near 100% penetrance.⁸

The variability in ECG findings and in the clinical histories in different families does suggest underlying genetic heterogeneity, which may be increasing as further Romano-Ward-like disorders are lumped under this heading (for example, recurrent polymorphic VT with normal QTc⁹ and bradycardia dependent long QT syndrome¹⁰). The finding of genetic linkage to two different chromosomes in different families,^{11,12} and to neither in others^{13,14} also suggests underlying heterogeneity.

With regard to treatment, while it is certainly true to say that β -blockade reduces the frequency of arrhythmias, it is not true to state that cardiac arrest (however defined) never occurs in medically treated affected subjects. At least one case of death while on a β -blocker has been published,¹⁵ and the prospective international study of 328 families reported by Moss *et al*¹⁶ found that 9/147 patients who died under the age of 50 (from presumed cardiac arrhythmias) were on antiadrenergic therapy (β -blockers or left cervical sympathetic ganglionectomy or both). Moss *et al*¹⁷ have also reported on the efficacy of permanent pacemakers in those patients with long QT syndrome whose symptoms and arrhythmias are not abolished by antiadrenergic therapy. This accords with our experience, where two members of one family have required the addition of permanent pacemaker therapy to abolish their episodic ventricular tachycardias,¹⁸ and this is now a well established treatment.¹⁹

In summary, we agree with the conclusion of Reardon *et al*¹ that counselling in the long QT syndromes is not straightforward. It is complicated by heterogeneity of severity, penetrance, and ECG findings, and also by genetic heterogeneity. We agree that assignment of a subject's status should not be by QTc alone, but suggest that it should include an assessment of the T/U wave morphology in

the light of the family ECG pattern, in addition to clinical assessment of symptoms. There may be some guide to prognosis from the family history, and from a subject's past history and sex (previous symptoms and female sex are strong risk factors for future cardiac events¹⁶). The benefits of modern therapy for affected patients, at risk for arrhythmias and sudden death, are such that careful family investigation and counselling, with treatment where appropriate, are strongly advised, despite the difficulties outlined above.

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