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# The IG Clinic

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**MEDICAL REPORT**

**Re: Ani Mihailova dob: 18/12/07 P31/190**
**[redacted], Burgas, Bulgaria**

I reviewed this five year old girl who is the second born child to this non consanguineous couple from Bulgaria. Ani's older brother acted as interpreter. There is no other family history of note and both parents are well without problems. They have had eye examinations but not formal electrical stimulation testing.

There is no history of any miscarriages or infertility.

In Bulgaria it was recognized that Ani had initially got congenital hypothyroidism and has been treated with L-thyroxine from day 21. Birth weight was 3.25kg and at birth because she had horizontal nystagmus she was investigated further and identified as having bilateral optic atrophy. Currently she continues with poor vision, horizontal nystagmus and reduced vision; she is approximately -15 and -20.

She was said in Bulgaria to have mitral prolapse and this has understandably caused some concern and they also note that she has hypermobility. There also appears to be spina bifida occulta for which she has not had any treatment and because of this has a slight scoliosis.

The parents are concerned that Ani may have Marfan's syndrome although they realize the problems with the eyes is a visual disturbance of the retina or optic nerve rather than any lens dislocation.

The parents are to some degree confused about the eye findings as on the one hand they have been told it is cone rod dystrophy and on the other that it is possibly optic atrophy. They are certainly keen to know what the diagnosis is.

On examination Ani's height is on the 75$^{th}$ centile, head on the 50th. Arm span is 103cm, height 112.5cm. She is not disproportionate. Weight 17kg. She does have quite marked joint laxity with a Beighton score of 9/9. There are spread scars on the body. The uvula is normal. Palate is unremarkable. There is a scoliosis, concave to the left and her chest is asymmetrical. She has normal hands and legs. There is no evidence of any bruising or varicose veins and she doesn't have overly visible veins. Skin texture appears normal. She does have slightly deep set eyes however.

The heart sounds were normal that I could hear.

I reassured the parents that I really don't think this young girl has Marfan's syndrome and certainly doesn't fulfil the Ghent criteria.

However given the past history of the mitral lesion and the parental concerns it would be extremely prudent to have her reviewed by Professor Deanfield.

I understand that an echocardiogram done under his care has shown no significant problem with the heart and certainly no major regurgitation or prolapse. He has given the parents advice by separate letter.

In order to try and clarify if this was cone rod dystrophy which would be one spectrum of genes or whether this is optic atrophy I have arranged for repeat ERG with VEPS under the care of Mr Liasis at GOSH. This has shown changes compatible with optic atrophy.

I am not able to identify a single unifying syndrome that would connect the optic atrophy with joint laxity in the context of completely normal mental development and no other dysmorphic features.

We do have three common mutations in the gene for Leber's hereditary optic neuropathy (LHON) that account for over 80% of all the mutations in Caucasian parents and I have recommended to the family that we do this.

Clearly they are concerned that all is done for testing but if the LHON gene testing proves to be negative then I will go on to do the full 105 gene panel for cone rod dystrophy. This panel also includes the genes for Leber's congenital amaurosis.

I discussed with the parents that this is most likely a new dominant mutation in the OPA1 gene causing Leber's hereditary optic neuropathy (LHON). The prevalence of LHON mutations is approximately 1:500 and numerous trials have been undertaken to try and preserve vision in such patients. IDEBENONE treatment which has an effect on mitochondrial function has been said to have a modest effect in half the cases. There is some evidence, albeit weak, for the use of UBIQUIONE (co-enzyme Q10) but the strongest evidence is for avoiding smoking and where possible excessive alcohol intake.

There have of course been other trials using different compounds such as Vitamin E but the data for this is yet to emerge.

There are certain foods which are said to be best avoided in LHON but the evidence for this is extremely small and I have given the family some details of this.

I would recommend that they see their ophthalmologist in Bulgaria about these potential treatments and discuss further any potential value in a trial of treatment or joining a more formal international trial.

In summary therefore I think this girl has LHON which is a new dominant mutation, rather than being inherited from one of the parents. I have advised that there is therefore a 50% chance that she may pass this down to any children she may have and that prenatal testing would be available as and when Ani wanted this. Clearly before she has a family she needs to see a clinical geneticist to

get further advice.

Ani's parents are not planning any further children and they understand that the optic atrophy and visual loss is likely to be progressive.

They are seemingly well supported in Bulgaria and I have not made further arrangements to review them in clinic but I would be delighted to see them again if things change and for a joint hypermobility and cardiac review in 3-5 years' time.

It is probably worth saying at this point that the hypermobility fits in very well with an Ehlers Danlos type 3 pattern and we have no gene test available for this. I have given some general advice about joint care but most sports at school are perfectly acceptable. In the longer term non-weight bearing sports such as swimming or cycling should be encouraged. Ani does have some degree of pronation in her feet, particularly the left side and I have suggested the parents start using some gel inserts in her shoe, together with buying shoes that have ankle support and take care in buying correct exercise shoes/trainers that give ankle support and prevent pronation.

Unfortunately dominant optic atrophy is characterised by insidious onset and progression of visual impairment in early childhood with moderate to severe loss in visual acuity.

The main problem is the diffused atrophy and loss of the ganglion cell layer of the retina and the loss of myelin and nerve tissue within the optic nerve. The cone and rod receptors in themselves are normal. There is of course a lot of individual variability, but Ani does seem to be following along the more classical course.

At the moment I have been reassuring and there is much for the parents to be doing to improve Ani's learning situation and also things to implement to protect her joints for the future. I look forward to seeing them again in 3-5 years time.

Yours sincerely

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cc.

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